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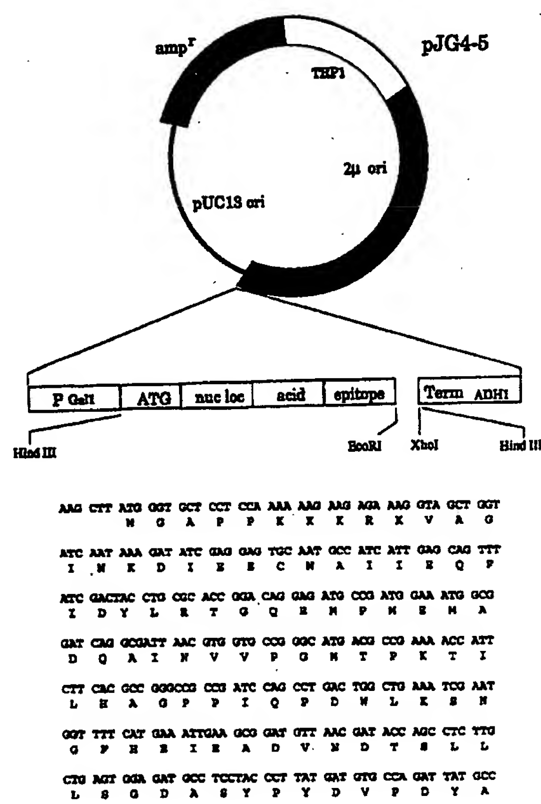
(57) Abstract

The present invention relates to the discovery of novel proteins of mammalian origin which can associate with the human cyclin dependent kinase 4 (CDK4).



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CDK4 Binding Proteins

Background of the Invention

Passage of a mammalian cell through the cell cycle is regulated at a number of key control points. Among these are the points of entry into and exit from quiescence (G_0), the restriction point, the G_1/S transition, and the G_2/M transition (for review, see Draetta (1990) *Trends Biol Sci* 15:378-383; and Sherr (1993) *Cell* 73:1059-1065). For a cell to pass through a control point and enter the next phase of the cell cycle, it must complete all of the events of the preceding cell cycle phase and, in addition, satisfy a number of check-point controls. Such controls act, for example, to ensure that DNA replication has been successfully completed before the onset of mitosis. Ultimately, information from these check-point controls is integrated through the regulated activity of a group of related kinases, the cyclin-dependent kinases (CDKs). Once a phase of the cell cycle has been successfully completed, phosphorylation of a critical substrates by activated CDKs allow passage of a cell cycle transition point and execution of the next cell cycle phase.

The ordered activation of the different CDKs constitutes the basic machinery of the cell cycle. The activity of CDKs is controlled by several mechanisms that include stimulatory and inhibitory phosphorylation events, and complex formation with other proteins. To become active, CDKs require the association of a group of positive regulatory subunits known as cyclins (see, for example, Nigg (1993) *Trends Cell Biol.* 3:296). In particular, human CDK4 exclusively associates with the D-type cyclins (D1, D2, and D3) (Xiong et al. (1992) *Cell* 71:505; Xiong et al. (1993) *Genes and Development* 7:1572; and Matsushime et al. (1991) *Cell* 65:701) and, conversely, the predominant catalytic partner of the D-type cyclins is the CDK4 kinase (Xiong et al. (1992) *Cell*). The complexes formed by CDK4 and the D-type cyclins have been strongly implicated in the control of cell proliferation during the G1 phase (Motokura et al. (1993) *Biochem. Biophys. Acta.*1155:63-78; Sherr (1993) *Cell* 73:1059-1065; Matsushimi et al. (1992) *Cell* 71:323-334); and Kamb et al. (1994) *Science* 264:436-440).

Summary of the Invention

The present invention relates to the discovery of novel proteins of mammalian origin which can associate with the human cyclin dependent kinase 4 (CDK4). As described herein, a CDK4-dependent interaction trap assay was used to isolate a number of proteins which bind CDK4, and which are collectively referred to herein as "CDK4-binding proteins" or "CDK4-

BPs". In particular embodiments of the present invention, human genes have been cloned for an apparent kinase (clone #225), an apparent isopeptidase (clone #269), an apparent protease (clone #71), a human cdc37 (clone # 269), a selectin-like protein (clone #11). The present invention, therefore, makes available novel proteins (both recombinant and purified forms), recombinant genes, antibodies to the subject CDK4-binding proteins, and other novel reagents and assays for diagnostic and therapeutic use.

One aspect of the invention features a substantially pure preparation of a CDK4-binding protein, or a fragment thereof. In preferred embodiments: the protein comprises an amino acid sequence at least 70% homologous to the amino acid sequence represented by one of SEQ ID Nos. 25-48; the polypeptide comprises an amino acid sequence at least 80% homologous to the amino acid sequence represented by one of SEQ ID Nos. 25-48; the polypeptide comprises an amino acid sequence at least 90% homologous to the amino acid sequence of one of SEQ ID Nos. 25-48; the polypeptide comprises an amino acid sequence identical to the amino acid sequence of one of SEQ ID Nos. 25-48. In a preferred embodiment: the fragment comprises at least 5 contiguous amino acid residues of one of SEQ ID Nos. 25-48; the fragment comprises at least 20 contiguous amino acid residues of one of SEQ ID Nos. 25-48; the fragment comprises at least 50 contiguous amino acid residues of one of SEQ ID Nos. 25-48. In a preferred embodiment, the fragment comprises at least a portion of the CDK4-BP which binds to a CDK, e.g. CDK4, e.g. CDK6, e.g. CDK5.

Yet another aspect of the present invention concerns an immunogen comprising the CDK4-binding protein, or a fragment thereof, in an immunogenic preparation, the immunogen being capable of eliciting an immune response specific for the subject CDK4-BP; e.g. a humoral response, eg. an antibody response; e.g. a cellular response.

A still further aspect of the present invention features an antibody preparation specifically reactive with an epitope of the CDK4-BP immunogen.

Another aspect of the present invention features a recombinant CDK4-binding protein, or a fragment thereof, comprising an amino acid sequence which is preferably: at least 70% homologous to one of SEQ ID Nos. 25-48; at least 80% homologous to one of SEQ ID No. 25-48; at least 90% homologous to one of SEQ ID No. 25-48. In a preferred embodiment, the recombinant CDK4-BP functions in one of either role of an agonist of cell cycle regulation or an antagonist of cell cycle regulation.

In one embodiment, the subject CDK4-BP is a protease. In preferred embodiments: the protease mediates degradation of cellular proteins, e.g. cell-cycle regulatory proteins, e.g. CDK4-associated proteins, e.g. cyclins, e.g. D-type cyclins; the protease affects the cellular half-life of a cell-cycle regulatory protein, e.g. a CDK-associated protein, e.g. a cyclin, e.g. a D-type cyclin, e.g. in normal cells, e.g. in cancerous cells.

In another embodiment, the subject CDK4-BP is a kinase, e.g., a stress-activated protein kinase.

In another embodiment, the subject CDK4-BP is a *Tre* oncoprotein, e.g. an isopeptidase, e.g. a deubiquitinating enzyme.

In yet another embodiment, the CDK4-binding protein is a human homolog of the yeast cdc37 gene., e.g. a protein which functions to control cell-cycle progression by integrating extracellular stimulus into cell-cycle control.

In a still further embodiment, the CDK4-binding protein is an adhesion molecule, e.g. related to a selectin, e.g. which is responsible for integrating information from surrounding cell-cell contacts into a checkpoint control.

In yet other preferred embodiments, the recombinant CDK4-binding protein is a fusion protein further comprising a second polypeptide portion having an amino acid sequence from a protein unrelated the CDK4-binding protein. Such fusion proteins can be functional in an interaction trap assay.

Another aspect of the present invention provides a substantially pure nucleic acid comprising a nucleotide sequence which encodes a CDK4-binding protein, or a fragment thereof, including an amino acid sequence at least 70% homologous to one of SEQ ID Nos. 25-48. In a more preferred embodiment, the nucleic acid encodes a protein comprising an amino acid sequence at least 70% homologous to one of SEQ ID Nos. 25-28; and more preferably at least 80% homologous to one of SEQ ID No. 25-28.

In yet a further preferred embodiment, the nucleic acid which encodes a CDK4-binding protein of the present invention, or a fragment thereof, hybridizes under stringent conditions to a nucleic acid probe corresponding to at least 12 consecutive nucleotides of SEQ ID Nos. 1-24 and 49-66; more preferably to at least 20 consecutive nucleotides of said SEQ ID listings; more preferably to at least 40 consecutive nucleotides of said SEQ ID listings. In a preferred embodiment, the nucleic acid which encodes a CDK4-binding protein of the present invention is provided by ATCC deposit 75788.

Furthermore, in certain preferred embodiments, nucleic acids encoding one of the subject CDK4-binding protein may comprise a transcriptional regulatory sequence, e.g. at least one of a transcriptional promoter or transcriptional enhancer sequence, operably linked to the CDK4-BP gene sequence so as to render the gene sequence suitable for use as an expression vector. In one embodiment, the CDK4-BP gene is provided as a sense construct. In another embodiment, the CDK4-BP gene is provided as an anti-sense construct.

The present invention also features transgenic non-human animals, e.g. mice, rabbits and pigs, which either express a heterologous CDK4-BP gene, e.g. derived from humans, or which mis-express their own homolog of a CDK4-BP gene, e.g. expression of the mouse homolog of the clone #71 protease is disrupted, e.g. expression of the mouse homolog of the clone #116 isopeptidase is disrupted, e.g. expression of the mouse homolog of the clone #225 kinase is disrupted, e.g. expression of the mouse homolog of the clone #269 cdc37 is disrupted. Such a transgenic animal can serve as an animal model for studying cellular disorders comprising mutated or mis-expressed CDK4-BP genes.

The present invention also provides a probe/primer comprising a substantially purified oligonucleotide, wherein the oligonucleotide comprises a region of nucleotide sequence which hybridizes under stringent conditions to at least 10 consecutive nucleotides of sense or antisense sequence of one of SEQ ID Nos. 1-24 and 49-66, or naturally occurring mutants thereof. In preferred embodiments, the probe/primer further comprises a label group attached thereto and able to be detected, e.g. the label group is selected from a group consisting of radioisotopes, fluorescent compounds, enzymes, and enzyme co-factors. Such probes can be used as a part of a diagnostic test kit for identifying transformed cells, such as for measuring a level of a CDK4-BP nucleic acid in a sample of cells isolated from a patient; e.g. measuring a CDK4-BP mRNA level in a cell; e.g. determining whether a genomic CDK4-BP gene has been mutated or deleted.

Another aspect of the present invention provides a method of determining if a subject, e.g. a human patient, is at risk for a disorder characterized by unwanted cell proliferation, comprising detecting, in a tissue of the subject, the presence or absence of a genetic lesion characterized by at least one of (i) a mutation of a gene encoding a CDK4-binding protein, or a homolog thereof; or (ii) the mis-expression of the CDK4-BP gene. In preferred embodiments: detecting the genetic lesion comprises ascertaining the existence of at least one of a deletion of one or more nucleotides from the gene, an addition of one or more nucleotides to the gene, an substitution of one or more nucleotides of the gene, a gross chromosomal rearrangement of the gene, a gross alteration in the level of a messenger RNA transcript of the gene, the presence of a non-wild type splicing pattern of a messenger RNA transcript of the gene, or a non-wild type level of the protein. For example, detecting the genetic lesion can comprise (i) providing a probe/primer comprising an oligonucleotide containing a region of nucleotide sequence which hybridizes to a sense or antisense sequence of one of SEQ ID Nos. 1-24 and 49-66, or naturally occurring mutants thereof, or 5' or 3' flanking sequences naturally associated with the gene; (ii) exposing the probe/primer to nucleic acid of the tissue; and (iii) detecting, by hybridization of the probe/primer to the nucleic acid, the presence or absence of the genetic lesion; e.g. wherein detecting the lesion comprises utilizing the probe/primer to determine the nucleotide sequence of the CDK4-BP

gene and, optionally, of the flanking nucleic acid sequences; e.g. wherein detecting the lesion comprises utilizing the probe/primer in a polymerase chain reaction (PCR); e.g. wherein detecting the lesion comprises utilizing the probe/primer in a ligation chain reaction (LCR). In alternate embodiments, the level of the protein is detected in an immunoassay.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims. The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, *Molecular Cloning A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press:1989); *DNA Cloning*, Volumes I and II (D. N. Glover ed., 1985); *Oligonucleotide Synthesis* (M. J. Gait ed., 1984); Mullis et al. U.S. Patent No. 4,683,195; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal Cells* (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*, Vols. 154 and 155 (Wu et al. eds.), *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

Brief Description of the Figure

Figure 1 illustrates the pJG4-5 library plasmid and the invariant 107 amino acid moiety it encodes. This moiety carries (amino to carboxy termini) an ATG, an SV40 nuclear localization sequence (PPKKKRKVA), the B42 transcription activation domain, and the HA1 epitope tag (YPYDVPDYA). pJG4-5 directs the synthesis of proteins under the control of the GAL1 promoter. It carries a 2μ replicator and a $TRP1^+$ selectable marker. Each of the CDK4 binding proteins of ATCC deposit accession number 75788 are inserted as EcoRI-XhoI fragments. Downstream of the XhoI site, pJG4-5 contains the ADH1 transcription terminator.

Figure 2 is a table demonstrating the interaction of each of the CDK-binding proteins with other cell cycle proteins.

Figure 3 is a table demonstrating the pattern of tissue expression for the mRNA encoding each of the subject CDK4-binding protein, as well as the message size.

Detailed Description of the Invention

The division cycle of eukaryotic cells is regulated by a family of protein kinases known as the cyclin-dependent kinases (CDKs). The sequential activation of individual members of this family and their consequent phosphorylation of critical substrates promotes orderly progression through the cell cycle. For example, the complexes formed by the *cyclin-dependent kinase 4* (CDK4) and the D-type cyclins have been strongly implicated in the control of cell proliferation during the G1 phase, and are strong candidates for oncogenes that could be major factors in tumorigenesis. Indeed, recent evidence suggests the possibility that CDK4 may serve as a general activator of cell division in most, if not all, cells.

The present invention, as set out below, derives from the discovery that, in addition to cyclins, p21, p16, and PCNA proteins, CDK4 is also associated with several other cellular proteins (hereinafter termed "CDK4-binding proteins" or "CDK4-BPs"), which associations are important to the regulation of cell growth, cell proliferation, and/or cell differentiation.

As described herein, a CDK4-dependent interaction trap assay was used to identify proteins that can associate with human CDK4. Surprisingly, a number of proteins were identified which interact with CDK4, and were subsequently cloned from a G_0 fibroblast cDNA library. Given the central role of CDK4 early in G_1 phase, the present data suggest that CDK4 is an important multiplex receiver of signal transduction data, with multiple pathways converging on it to control various aspects of the kinases's activity, including both catalytic activity and substrate specificity. Thus, because each of the proteins identified herein act close to the point of CDK4 process control, such as by channeling converging upstream signals to CDK4 or demultiplexing the activation of the CDK4 kinase activity by directing divergent downstream signal propagation from CDK4, each of the subject proteins is a potential therapeutic target for agents capable of modulating cell proliferation and/or differentiation.

The present invention, therefore, makes available novel assays and reagents for therapeutic and diagnostic uses. Moreover, drug discovery assays are provided for identifying agents which can affect the binding of one of the subject CDK-binding proteins with another cell-cycle regulatory protein, or which inhibit an enzymatic activity of the subject CDK4-binding protein. Such agents can be useful therapeutically to alter the growth and/or differentiation a cell.

To further illustrate, the clone designated #71 (Table 1 and Figure 2), corresponding to the protein represented by SEQ ID No. 31 (encoded by the nucleic acid of SEQ ID No. 7), shares certain homology with ATP-dependent proteases and is strongly suspected of possessing proteolytic activity. Accordingly, this protease may be is a protease involved in degradation of cell-cycle regulatory proteins, e.g. G1-cyclins such as cyclin D1, D2 or D3. Thus, clone 71 may be involved in regulating the cellular levels of other CDK4- or CDK6-associated proteins. For instance, the subject protease could be recruited by its interaction with CDK4 or CDK6 to a CDK4/cyclin D or CDK6/cyclin D complex in order to cause degradation of a D-type cyclin (e.g. cyclin D1). Such degradation would release the CDK for subsequent binding to another G_1 cyclin. Thus, agents which disrupt the binding of the protease to CDK4 or CDK6 can be used to prevent the proteolytic destruction of certain CDK4 or CDK6 associated cyclins, e.g. effectively increases the half-life of such cyclins. Alternatively, the present invention, by providing purified and/or recombinant forms of the protease, also facilitates identification of agents which act as mechanistic inhibitors of the protease and inhibit its proteolytic action on its substrates irrespective of its ability to bind CDK. As described in U.S. Patent Application No. 08/227,850 entitled "D1 Cyclin in G_1 Progression of Cell Growth, and Uses Related Thereto", the ability to increase the cellular level of cyclin D1, such as by inhibiting its proteolysis, can be useful in preventing unwanted cell growth in certain proliferative disorders.

In another embodiment, the CDK4-binding protein is an isopeptidase, such as a de-ubiquitinating enzyme. For instance, the clone designated #116 (Table 1 and Figure 2), corresponding to the polypeptide represented by SEQ ID. No. 33 (encoded by the nucleic acid of SEQ ID No. 9) shares certain homology with previously described *Tre* oncogenes and isopeptidases, and may function as a de-ubiquitinating enzyme. As is generally understood, the activities of several cellular proteins are reversibly regulated by ubiquitination and a successive de-ubiquitination steps such that the half-life of the protein, or allosteric control of its biological function, is fine tuned by the control of the level of ubiquitination of that protein. For example, as described above, cyclin degradation by ubiquitin-mediated proteolysis is an important step in the progression of the cell cycle. Thus, the subject de-ubiquitinating enzyme may be involved in balancing the level of ubiquitinated cyclin D by antagonistically competing with ubiquitin conjugating enzymes. Thus, CDK4 may be used by the subject enzyme to provide proximity to a substrate such as cyclin D. Moreover, CDK4 may provide additional substrate proximity with other cell cycle regulatory proteins, such as those involved in regulation of Rb function. Agents which inhibit either the interaction of the de-ubquitinating enzyme with CDK4, or which mechanistically inhibit the enzyme, can be used to disrupt the balance of ubiquitination of certain regulatory proteins.

In yet another embodiment, the CDK4-binding protein is a kinase which acts on CDK4 or other proteins which bind CDK4. For instance, the clone designated #225, corresponding to the polypeptide represented by SEQ ID No. 43 (encoded by SEQ ID No. 19) shares certain homology with other kinases of the family of stress-activated protein kinases (SAPKs) or Jun kinases (JNKs). These kinases are activated in response to a variey of cellular stresses, including treatment with tumor-necrosis factor-alpha and interleukin-beta. Thus, the subject kinase may represent a novel mechanism by which G1 phase arrest is effected in response to cellular stress. The kinase may phosphorylate either CDK4 or the bound cyclin D (other CDK4 associated protein), causing inhibition of the CDK activity and cell-cycle arrest.

In still further embodiments, the CDK4-binding protein is related to an adhesion molecule, such as a selectin. For example, the pJG4-5-CDKBP clone #11, corresponding to the partially characterized protein represented by SEQ. ID No. 25 (encoded by SEQ. ID No. 1) shares approximately 50% homology with selectin proteins, adhesion molecules which are found on epitheleal and possibly lymphoid cells. Growth of normal diploid mammalian cells *in vitro*, and presumably *in vivo*, is strongly regulated by the actual cell density. Cell-cell contacts via specific plasma membrane glycoproteins has been found to be a main growth regulatory principle. Malignant growth is suggested to result from impaired function of the signal transduction pathways connected with these membrane proteins. Moreover, it has been previously noted that a major control point in fibroblast cell cycle exists at the G_0-G_1 transition and is regulated by extracellular signals including contact inhibition (Han et al. (1993) *J. Cell Biol.* 122:461-471). It is asserted here that the subject adhesion molecule is responsible for integrating information from surrounding cell contacts into a checkpoint control. Consistent with this notion, nucleic acid hybridization experiments using a probe based on SEQ. ID No. 1 have detected clone 11 mRNA in normal primary fibroblasts (e.g., WI38 and IMR90), but that clone 11 mRNA levels become undetectable in SV40 Laze T transformed fibroblasts as well as fibrocarzinom or cell lines (e.g., Hs 913T cells) - each of which have lost contact inhibition and are able to form foci. Thus, the interaction of selectin-related proteins, such as clone 11, with CDKs (e.g., CDK4, CDK5 or CDK6) is a potential therapeutic target for design of agents capable of modulating proliferation and/or differentiation. In some instances, agents which restore the function of such selectin-like proteins will be desirable to inhibit proliferation. For example, peptidomimetics based on clone 11 sequences which bind CDK4, or gene therapy vehicles which deliver the clone 11 gene, can be used to mimic the function of the wild type protein and slow progression of the cell through the G_1 phase. For instance, in addition to treatment of cancer, such agents may be used to treat hypertension, diabetic macroangiopathy or artherosclerosis, where numerous abnormalities in vascular smooth-muscle cell (vsmc) growth is a common pathology resulting from abnormal contact inhibition and accelerated entry into the S phase.

Conversely, agents which bind clone #11 and/or other related selectins and prevent binding to a CDK can be used to prevent contact inhibition and therefore enhance proliferation (and potentially inhibit differentiation). For instance, such agents can be used to relieve contact inhibition of chondrocytes, particularly fibrochondrocytes, in order to facilitate de-differentiation of these cells into chondroblast cells which produce cartilage. Thus, therapeutic agents can be identified in assays using the subject protein which are useful in the treatment of connective tissue disorders, including cartilage repair.

In similar fashion, the CDK4-binding proteins designated as clone 61 and clone 190 are homologous to other cytoskeletal elements, such as tensin and actin-binding proteins, respectively. Recent evidence suggests that certain cytoskeletal proteins not only maintain structural integrity or provide motility for a cell, but might also be associated with signal transduction. Tensin, for example, has been implicated in signal transduction, as well as the anchor for actin filaments at the focal adhesion. Accordingly, the association of CDK4 and clones 61 and 190 can be implicated, as above, in mediating such membane-induced events as contact inhibition, etc., such interaction being a therapeutic target for modulating, for example, cell adhesion and de-adhesion and ivadopodia (e.g., invasion into the extracellular matrix) by normal and transformed cells. The interaction between these molecules and CDK4 can be one wherein CDK4 is a downstream target for apparent affector molecules. Alternatively, these proteins can be substrates for CDK complexes, the phosphorylation affecting the structure or localization of the cytoskeletal elements.

In still further embodiments, the CDK4-binding protein is a DNA binding factor involved in regulation of transcription and/or replication. For example, clones 127 and 118 (see Table 1 and Figure 2) each appear to possess zinc-finger motifs which implicate them in DNA-binding. These proteins may function as downstream targets for activation or inactivation by CDK phosphorylation, and/or to localize a CDK to DNA. Moreover, the fact that clone 127 binds strongly to p53 and Rb (Figure 2) suggests an integrated role in the G_1 checkpoint(s). In yet another embodiment, the CDK4-binding protein is an mRNA-splicing factor. For instance, clone 216 is apparently such a protein, the function of which may be modulated by the action of a CDK, or which itself may modulate the activity of a CDK.

In another embodiment, the CDK4-binding protein contains a CDK consensus phosphorylation signal, and the CDK4-BP is a CDK4 substrate and/or an inhibitor of the CDK4 kinase activity. For example, each of clones #13, #22 and #227 contain such CDK consensus sequence. Thus, these cellular proteins can be downstream substrates of CDK4 (as well as CDK6 or CDK5). Additionally, the CDK4-BP, particularly the phosphoprotein form, can serve as an inhibitor of a CDK, such as CDK4. Thus, the phosphorylated CDK4-BP could serve as a feedback loop, either from CDK4 itself or from another CDK, acting to modulate the activity of a CDK to which it binds.

In still further embodiments, the CDK4-binding protein is a human homolog of the yeast Cdc37 gene (Ferguson et al. (1988) *Nuc. Acid Res.* 14:6681-6697; and Breter et al. (1983) *Mol. Cell Biol.* 3:881-891). In particular, one embodiment of the present application is directed to the association between CDK4 and a novel human protein which we identified as the mammalian homolog of the yeast gene Cdc37, (though only about 14 percent homologous) the mammalian gene being referred to herein as "*cdc37*".

Studies of the temperature-sensitive Cdc37-1 mutant in *Saccharonyces cerevisiae* suggests that Cdc37 is required for exit from G_1 phase of the cell-cycle (Reed (1980) *Genetics* 95:561-577; and Ferguson et al. (1986) *Nuc Acid Res* 14:6681-6697). Mutation or deletion in yeast of the Cdc37 gene results in arrest at "START", the regulatory point in the yeast cell-cycle which in many ways resembles the G_1 restriction point and G_1/S checkpoint in mammalian cells.

While the precise function of Cdc37 in yeast is not known, our observation of the human *cdc37* binding to CDK4 and CDK6 provides an explanation for the G_1 phase arrest in Cdc37-1 mutant yeast cells, and also for the role of *cdc37* in mammalian cells. It is asserted herein that the mammalian *cdc37*, and presumably the yeast Cdc37, is required for activation of cyclin-dependent kinases. The *cdc37* gene product may be required for stabilization or localization of CDKs such as CDK4, or may play a more general role in the regulation of the kinase activity, such as through allosteric regulation or a chaperon-like activity which facilitates assembly of multi-protein complexes with a CDK. While not wishing to be bound by any particular theory, our results in recombinant expression systems indicate that a transient complex is formed between, for example, CDK4, cyclin D1 and *cdc37*, with *cdc37* dissociating upon phosphorylation of CDK4 by a CDK-activating kinase (CAK).

Futhermore, we have observed that the *cdc37* protein itself is apparently regulated, at least in part, by phosphorylation, the phosphorylated form evidently mediating the interaction of, for example, CDK4 and cyclin D1. Using immobilized *cdc37*, several proteins which bind to *cdc37* were purified, e.g. by *cdc37* chromatography. Detecting phosphorylation of a *cdc37* substrate, a kinase activity was eluted from the *cdc37* column under a salt gradiant. The active fractions were pooled, and separated by gel electrophoresis, and an in-gel kinase assay was performed. Five bands, approximate molecular weights of 40kd, 42kd, 95kd, 107kd and 117kd, were identified in the gel as having kinase activity towards *cdc37*. Two of the five bands appeared as a doublet, each having a molecular weight of approximately 40 kd. This pattern has been observed previously in the literature for various members of the *erk* kinase family (for review, see Cobb et al. (1994) *Semin Cancer Biol* 5:261-8), which kinases are involved in signal transduction, especially from mitogenic signals. For instance, transforming agents utilize this cascade in inducing cell proliferation. Indeed, western blot analysis revealed that these two kinase bands isolated by *cdc37* binding were the *erk-1* and

erk-2 kinases, and immunopurified forms of each of these serine/threonine kinases was found to phosphorylate (and activate) *cdc37*.

Thus, it is understood by the present invention that the human *cdc37* functions to control cell-cycle progression, perhaps by integrating extracellular stimulus into cell-cycle control, and it is therefore expected that the CDK4-*cdc37*, CDK6-*cdc37* and *erk-cdc37* interactions can be a very important target for drug design. For instance, agents which disrupt the binding of a CDK and *cdc37*, e.g., CDK4 peptidomimetic which bind *cdc37*, could be used to effect the progression of cell through G_1. Moreover, antagonistic mutants of the subject *cdc37* protein, e.g., mutants which disrupt the function of the normal *cdc37* protein, can be provided by gene therapy in order to inhibit proliferation of cells. Furthermore, the fact that the human *cdc37* homolog binds Src and p53 supports the role of *cdc37* in cell-cycle checkpoints, as well as suggesting alternate therapeutic targets, e.g., the Src-*cdc37* or p53-*cdc37* interactions.

Furthermore, it is demonstrated here for the first time that p16 is able to associate with CDK6. Previously, p16 was believed to associate exclusively with CDK4 and acted as an inhibitor of the CDK4 kinase activity. The present data strongly suggests that p16 functions in the same or similar role with respect to CDK6. Thus, the interaction between p16 and CDK6 is a potential therapeutic target for agents which (i) disrupt this interaction; (ii) mimic this interaciton by binding CDK6 in a manner analogous to p16, e.g. p16 peptidomimetics which bind CDK6; or (iii) are mechanistic inhibitors of the CDK6 kinase activity. Moreover, as described below, the present invention provides differential screening assays for identifying agents which disrupt or otherwise alter the regulation of only one of either CDK4 or CDK6 without substantially affecting the other.

In general, polypeptides designated herein as CDK4-binding proteins refers to polypeptides that (i) have an amino acid sequence corresponding (identical or homologous) to all or a portion of an amino acid sequence of one of the subject CDK4-binding protein designated by SEQ ID Nos: 25-48 and (ii) which have at least one biochemical activity of that CDK4-binding protein. In preferred embodiments, a biological activity of a CDK4-binding protein can be characterized as including, in addition to those activities described above for individual clones, the ability to bind to a cyclin dependent kinase, preferably CDK4. The above notwithstanding, the biological activity of a CDK4-binding protein may be distinguished by one of more of the following attributes: an ability to regulate the cell-cycle of a eukaryotic cell, e.g. a mammalian cell cycle, e.g., a human cell cycle; an ability to regulate proliferation/cell growth of a eukaryotic cell, e.g. a mammalian cell, e.g., a human cell; an ability to regulate progression of a eukaryotic cell through G_1 phase, e.g. regulate progression of a mammalian cell from G_0 phase into G_1 phase, e.g. regulate progression of a mammalian cell through G_1 phase; an ability to regulate the kinase activity of a cyclin

dependent kinase, e.g. a CDK active in G_1 phase, e.g. CDK4, e.g. CDK6; an ability to regulate phosphorylation of an Rb or Rb-related protein by CDK4; an ability to regulate the effects of mitogenic stimulation on cell-cycle progression, e.g. regulate contact inhibition, e.g. mediate growth factor- or cytokine-induced mitogenic stimulation, e.g. regulate paracrine-responsiveness. Certain of the CDK4-binding proteins of the present invention may also have biological activities which include an ability to suppress tumor cell growth, e.g. in a tumor cell which has lost contact inhibition, e.g. in tumor cells which have paracrine feedback loops. Other biological activities of the subject CDK4-binding proteins are described herein or will be reasonably apparent to those skilled in the art. Moreover, according to the present invention, a polypeptide has biological activity if it is a specific agonist or antagonist of a naturally-occurring form of a CDK4-binding protein.

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single-stranded (such as sense or antisense) and double-stranded polynucleotides.

As used herein, the term "gene" or "recombinant gene" refers to a nucleic acid comprising an open reading frame encoding a *CDK4-binding protein* of the present invention, including both exon and (optionally) intron sequences. The term "intron" refers to a DNA sequence present in a given *cdc37* gene which is not translated into protein and is generally found between exons.

As used herein, the term "transfection" means the introduction of a nucleic acid, e.g., an expression vector, into a recipient cell by nucleic acid-mediated gene transfer. "Transformation", as used herein, refers to a process in which a cell's genotype is changed as a result of the cellular uptake of exogenous DNA or RNA, and, for example, the transformed cell expresses a recombinant form of on of the subject CDK4-binding proteins, or where anti-sense expression occurs from the transferred gene, the expression of a naturally-occurring form of the *CDK4-binding protein* is disrupted.

As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of preferred vector is an episome, i.e., a nucleic acid capable of extra-chromosomal replication. Preferred vectors are those capable of autonomous replication and/expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility

in recombinant DNA techniques are often in the form of "plasmids" which refer to circular double stranded DNA loops which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

"Transcriptional regulatory sequence" is a generic term used throughout the specification to refer to DNA sequences, such as initiation signals, enhancers, and promoters, which induce or control transcription of protein coding sequences with which they are operably linked. In preferred embodiments, transcription of a recombinant gene is under the control of a promoter sequence (or other transcriptional regulatory sequence) which controls the expression of the recombinant gene in a cell-type in which expression is intended. It will also be understood that the recombinant gene can be under the control of transcriptional regulatory sequences which are the same or which are different from those sequences which control transcription of the naturally-occurring form of the *CDK4-binding protein.*

As used herein, the term "tissue-specific promoter" means a DNA sequence that serves as a promoter, i.e., regulates expression of a selected DNA sequence operably linked to the promoter, and which effects expression of the selected DNA sequence in specific cells of a tissue, such as cells of a urogenital origin, e.g. renal cells, or cells of a neural origin, e.g. neuronal cells. The term also covers so-called "leaky" promoters, which regulate expression of a selected DNA primarily in one tissue, but cause expression in other tissues as well.

As used herein, a "transgenic animal" is any animal, preferably a non-human mammal, a bird or an amphibian, in which one or more of the cells of the animal contain heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or *in vitro* fertilization, but rather is directed to the introduction of a recombinant DNA molecule. This molecule may be integrated within a chromosome, or it may be extrachromosomally replicating DNA. In the typical transgenic animals described herein, the transgene causes cells to express a recombinant form of *a CDK4-binding protein*, e.g. either agonistic or antagonistic forms. However, transgenic animals in which the recombinant gene is silent are also contemplated, as for example, the FLP or CRE recombinase dependent constructs described below. The "non-human animals" of the invention include vertebrates such as rodents, non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc. Preferred

non-human animals are selected from the rodent family including rat and mouse, most preferably mouse, though transgenic amphibians, such as members of the *Xenopus* genus, and transgenic chickens can also provide important tools for understanding, for example, embryogenesis and tissue patterning. The term "chimeric animal" is used herein to refer to animals in which the recombinant gene is found, or in which the recombinant is expressed in some but not all cells of the animal. The term "tissue-specific chimeric animal" indicates that the recombinant gene is present and/or expressed in some tissues but not others.

As used herein, the term "transgene" means a nucleic acid sequence (encoding, e.g., a *cdc37* polypeptide or other CDK4-BP), which is partly or entirely heterologous, i.e., foreign, to the transgenic animal or cell into which it is introduced, or, is homologous to an endogenous gene of the transgenic animal or cell into which it is introduced, but which is designed to be inserted, or is inserted, into the animal's genome in such a way as to alter the genome of the cell into which it is inserted (e.g., it is inserted at a location which differs from that of the natural gene or its insertion results in a knockout). A transgene can include one or more transcriptional regulatory sequences and any other nucleic acid, such as introns, that may be necessary for optimal expression of a selected nucleic acid.

As is well known, genes for a particular polypeptide may exist in single or multiple copies within the genome of an individual. Such duplicate genes may be identical or may have certain modifications, including nucleotide substitutions, additions or deletions, which all still code for polypeptides having substantially the same activity. The term "DNA sequence encoding a *CDK4-binding protein*" may thus refer to one or more genes within a particular individual. Moreover, certain differences in nucleotide sequences may exist between individual organisms, which are called alleles. Such allelic differences may or may not result in differences in amino acid sequence of the encoded polypeptide yet still encode a protein with the same biological activity.

"Homology" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences.

"Cells," "host cells" or "recombinant host cells" are terms used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny

may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A "chimeric protein" or "fusion protein" is a fusion of a first amino acid sequence encoding one of the subject *CDK4-binding proteins* with a second amino acid sequence defining a domain foreign to and not substantially homologous with any domain of the polypeptide making up the first sequence. A chimeric protein may present a foreign domain which is found (albeit in a different protein) in an organism which also expresses the first protein, or it may be an "interspecies", "intergenic", etc. fusion of protein structures expressed by different kinds of organisms.

The term "evolutionarily related to", with respect to nucleic acid sequences encoding each of the subject CDK4-binding proteins, refers to nucleic acid sequences which have arisen naturally in an organism, including naturally occurring mutants. The term also refers to nucleic acid sequences which, while derived from a naturally occurring gene, have been altered by mutagenesis, as for example, combinatorial mutagenesis described below, yet still encode polypeptides which have at least one activity of a CDK4-binding protein.

The term "isolated" as also used herein with respect to nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs, or RNAs, respectively, that are present in the natural source of the macromolecule. For example, isolated nucleic acids encoding the subject polypeptides preferably include no more than 10 kilobases (kb) of nucleic acid sequence which naturally immediately flanks a particular *CDK4-BP* gene in genomic DNA or mRNA, more preferably no more than 5kb of such naturally occurring flanking sequences, and most preferably less than 1.5kb of such naturally occurring flanking sequence. The term isolated as used herein also refers to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Moreover, an "isolated nucleic acid" is meant to include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state.

As described herein, one aspect of the invention pertains to an isolated nucleic acid having a nucleotide sequence encoding one of the subject CDK4-binding proteins, fragments thereof, and/or equivalents of such nucleic acids. The term equivalent is understood to include nucleotide sequences encoding functionally equivalent CDK4-binding proteins or functionally equivalent polypeptides which, for example, retain the ability to bind a CDK (e.g. CDK4), and which may additionally reatin other activities of a CDK4-binding protein such as described herein. Equivalent nucleotide sequences will include sequences that differ by one or more nucleotide substitutions, additions or deletions, such as allelic variants; and will also include sequences that differ from the nucleotide sequence encoding the presently

claimed CDK4-binding proteins shown in any of SEQ ID Nos: 1-24 or 49-70 due to the degeneracy of the genetic code. Equivalents will also include nucleotide sequences that hybridize under stringent conditions (i.e., equivalent to about 20-27°C below the melting temperature (T_m) of the DNA duplex formed in about 1M salt) to the nucleotide sequence of a CDK4-binding protein represented by one of SEQ ID Nos: 25-48, or to a nucleotide sequence of a CDK4-BP insert of the vector pJG4-5-CDKBP (ATCC accession no. 75788). In one embodiment, equivalents will further include nucleic acid sequences derived from, and evolutionarily related to, a nucleotide sequences shown in any of SEQ ID Nos: 1-24.

Moreover, it will be generally appreciated that, under certain circumstances, it may be advantageous to provide homologs of the subject CDK4-binding proteins which function in a limited capacity as one of either a CDK4-BP agonists or a CDK4-BP antagonists, in order to promote or inhibit only a subset of the biological activities of the naturally-occurring form of the protein. Thus, specific biological effects can be elicited by treatment with a homolog of limited function, and with fewer side effects relative to treatment with agonists or antagonists which are directed to all CDK4-BP related biological activities. Such homologs of the subject CDK4-binding proteins can be generated by mutagenesis, such as by discrete point mutation(s) or by truncation. For instance, mutation can give rise to homologs which retain the substantially same, or merely a subset, of the biochemical activity of the CDK4-BP from which it was derived. Alternatively, antagonistic forms of the protein can be generated which are able to inhibit the function of the naturally occurring form of the protein. For example, homologs can be made which, relative the authentic form of the protein, competitively bind to CDK4 or other upstream or downstream binding partners of the naturally occurring CDK4-BP, but which are not themselves capable of forming productive complexes for propagating an intracellular signal or the like. When expressed in the same cell as the wild-type protein, such antagonistic mutants could be, for example, analogous to a dominant negative mutation arising in the cell. To illustrate, the homologs of the clone #71 protease might be generated to retain a protease activity, or, conversely, engineered to lack a protease activity, yet retain the ability to bind CDK4. In the instance of the latter, the catalytically inactive protease can be used to competitively inhibit the binding to CDK4 of the naturally-occurring form of the protease. In similar fashion, clone #225 homologs can be provided which, for example, are catalytically inactive as kinases, yet which still bind to a CDK. Such homolog are likely to act antagonistically to the role of the natural enzyme in cell cycle regulation, and can be used, for example, to inhibit paracrine feedback loops. Likewise, clone #116 homologs can be generated which are not capable of mediating ubiquitin levels, yet which nevertheless competively bind CDK4 and therefore act antagonistically to the wild-type form of the isopeptidase when expressed in the same cell.

In one embodiment, the nucleic acid encodes a polypeptide which is a specific agonist (mimetic) or antagonist of a naturally occurring form of one of the subject CDK4-binding proteins. Preferred nucleic acids encode a polypeptide at least 70% homologous, more preferably 80% homologous and most preferably 85% homologous with an amino acid sequence shown in any of SEQ ID NOS: 25-48. Nucleic acids which encode polypeptides including amino acid sequences at least about 90%, more preferably at least about 95%, and most preferably indentical with a sequence shown in any of SEQ ID NOS: 25-48 are also within the scope of the invention.

Certain of the nucleotide sequences shown in SEQ ID Nos. 1-24 and 49-70 encode portions of the subject CDK4-binding proteins. Therefore, in a further embodiment of the invention, the recombinant CDK4-BP genes can further include, in addition to nucleotides encoding the amino acid sequence shown in SEQ ID Nos. 25-48, additional nucleotide sequences which encode amino acids at the C-terminus and N-terminus of each protein, though not shown in those sequence listings. For instance, a recombinant CDK4-BP gene can include nucleotide sequences of a PCR fragment generated by amplifying the one of the coding sequence of one of the CDK4-BP clones of pJG4-5-CDKBP using sets of primers derived from Table 1.

Another aspect of the invention provides a nucleic acid which hybridizes under high or low stringency conditions to a nucleic acid which encodes a polypeptide having all or a portion of an amino acid sequence shown in any of SEQ ID NOS: 25-48. Appropriate stringency conditions which promote DNA hybridization, for example, 6.0 x sodium chloride/sodium citrate (SSC) at about 45°C, followed by a wash of 2.0 x SSC at 50°C, are known to those skilled in the art or can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. For example, the salt concentration in the wash step can be selected from a low stringency of about 2.0 x SSC at 50°C to a high stringency of about 0.2 x SSC at 50°C. In addition, the temperature in the wash step can be increased from low stringency conditions at room temperature, about 22°C, to high stringency conditions at about 65°C.

Isolated nucleic acids encoding polypeptides, as described herein, and having a sequence which differs from the nucleotide sequence shown any of SEQ ID NOS: 1-24 due to degeneracy in the genetic code are also within the scope of the invention. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC each encode histidine) may result in "silent" mutations which do not affect the amino acid sequence of the CDK4-binding protein. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the subject CDK4-binding proteins will exist individuals. One skilled in the art will appreciate that these variations in one or more nucleotides (up to about

3-5% of the nucleotides) of the nucleic acids encoding a particular member of CDK4-BP family may exist among individuals of a given species due to natural allelic variation. Any and all such nucleotide variations and resulting amino acid polymorphisms are within the scope of this invention.

Fragments of the nucleic acids encoding a biologically active portion of the subject CDK4-binding proteins are also within the scope of the invention. As used herein, a nucleic acid "fragment" encoding a bioactive portion of a CDK4-binding protein refers to a nucleic acid having fewer nucleotides than the nucleotide sequence encoding the entire amino acid sequence of a CDK4-binding protein but which nevertheless encodes a polypeptide retaining at least a portion of the biochemical function of the full-length protein, or is a specific antagonist thereof. Nucleic acid fragments within the scope of the present invention include those capable of hybridizing under high or low stringency conditions with nucleic acids from other species for use in screening protocols to detect CDK4-BP homologs, as well as those capable of hybridizing with nucleic acids from human specimens for use in detecting the presence of a nucleic acid encoding one of the subject CDK4-BPs, including alternate isoforms, e.g. mRNA splicing variants. Nucleic acids within the scope of the invention may also contain linker sequences, modified restriction endonuclease sites and other sequences useful for molecular cloning, expression or purification of recombinant forms of the subject CDK4-binding proteins.

As indicated by the examples set out below, a nucleic acid encoding one of the subject CDK4-binding protein may be obtained from mRNA present in any of a number of eukaryotic cells. It should also be possible to obtain nucleic acids encoding the subject CDK4-binding proteins from genomic DNA obtained from both adults and embryos. For example, a gene encoding a CDK4-binding protein can be cloned from either a cDNA or a genomic library in accordance with protocols herein described, as well as those generally known to persons skilled in the art. For instance, a cDNA encoding one of the subject CDK4-binding proteins can be obtained by isolating total mRNA from a cell, e.g. a mammalian cell, e.g. a human cell, including tumor cells. Double stranded cDNAs can then be prepared from the total mRNA, and subsequently inserted into a suitable plasmid or bacteriophage vector using any one of a number of known techniques. A gene encoding a CDK4-binding protein can also be cloned using established polymerase chain reaction techniques in accordance with the nucleotide sequence information provided by the invention. The nucleic acid of the invention can be DNA or RNA. A preferred nucleic acid is: e.g. a cDNA comprising a nucleic acid sequence represented by any one of SEQ ID Nos: 1-24 and 49-70; e.g. a cDNA derived from the pJG4-5-CDKBP library of ATCC deposit no. 75788.

Another aspect of the invention relates to the use of the isolated nucleic acid in "antisense" therapy. As used herein, "antisense" therapy refers to administration or *in situ* generation of oligonucleotide probes or their derivatives which specifically hybridizes (e.g. binds) under cellular conditions, with the cellular mRNA and/or genomic DNA encoding a CDK4-binding protein so as to inhibit expression of that protein, e.g. by inhibiting transcription and/or translation. The binding may be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interactions in the major groove of the double helix. In general, "antisense" therapy refers to the range of techniques generally employed in the art, and includes any therapy which relies on specific binding to oligonucleotide sequences.

An antisense construct of the present invention can be delivered, for example, as an expression plasmid which, when transcribed in the cell, produces RNA which is complementary to at least a unique portion of the cellular mRNA which encodes a CDK4-binding protein. Alternatively, the antisense construct is an oligonucleotide probe which is generated *ex vivo* and which, when introduced into the cell causes inhibition of expression by hybridizing with the mRNA and/or genomic sequences encoding a CDK4-binding protein. Such oligonucleotide probes are preferably modified oligonucleotide which are resistant to endogenous nucleases, e.g. exonucleases and/or endonucleases, and is therefore stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patents 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy have been reviewed, for example, by van der Krol et al. (1988) *Biotechniques* 6:958-976; and Stein et al. (1988) *Cancer Res* 48:2659-2668.

Accordingly, the modified oligomers of the invention are useful in therapeutic, diagnostic, and research contexts. In therapeutic applications, the oligomers are utilized in a manner appropriate for antisense therapy in general. For such therapy, the oligomers of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remmington's Pharmaceutical Sciences, Meade Publishing Co., Easton, PA. For systemic administration, injection is preferred, including intramuscular, intravenous, intraperitoneal, and subcutaneous for injection, the oligomers of the invention can be formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, the oligomers may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included.

Systemic administration can also be by transmucosal or transdermal means, or the compounds can be administered orally. For transmucosal or transdermal administration,

penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration may be through nasal sprays or using suppositories. For oral administration, the oligomers are formulated into conventional oral administration forms such as capsules, tablets, and tonics. For topical administration, the oligomers of the invention are formulated into ointments, salves, gels, or creams as generally known in the art.

In addition to use in therapy, the oligomers of the invention may be used as diagnostic reagents to detect the presence or absence of the target DNA or RNA sequences to which they specifically bind.

This invention also provides expression vectors comprising a nucleic acid encoding one of the subject CDK4-binding proteins and operably linked to at least one transcriptional regulatory sequence. Operably linked is intended to mean that the nucleotide sequence is linked to a regulatory sequence in a manner which allows expression of the nucleotide sequence. Accordingly, the term regulatory sequence includes promoters, enhancers and other expression control elements. Exemplary regulatory sequences are described in Goeddel; *Gene Expression Technology*: *Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). For instance, any of a wide variety of expression control sequences-sequences that control the expression of a DNA sequence when operatively linked to it may be used in these vectors to express DNA sequences encoding the *cdc37* proteins of this invention. Such useful expression control sequences, include, for example, the early and late promoters of SV40, adenovirus or cytomegalovirus immediate early promoter, the lac system, the trp system, the TAC or TRC system, T7 promoter whose expression is directed by T7 RNA polymerase, the major operator and promoter regions of phage lambda , the control regions for fd coat protein, the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase, e.g., Pho5, the promoters of the yeast α-mating factors, the polyhedron promoter of the baculovirus system and other sequences known to control the expression of genes of prokaryotic or eukaryotic cells or their viruses, and various combinations thereof. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. Moreover, the vector's copy number, the ability to control that copy number and the expression of any other proteins encoded by the vector, such as antibiotic markers, should also be considered.

Still another aspect of the inventionc oncerns the use of expression constructs of the subject CDK4-binding proteins in methods by which it is administered in a biologically effective carrier, e.g. any formulation or composition capable of effectively transfecting cells

in vivo with a recombinant CDK4-BP gene. Approaches include insertion of the subject gene in viral vectors including recombinant retroviruses, adenovirus, adeno-associated virus, and herpes simplex virus-1, or recombinant bacterial or eukaryotic plasmids. Viral vectors can be used to transfect cells directly; plasmid DNA can be delivered with the help of, for example, cationic liposomes (lipofectin) or derivatized (e.g. antibody conjugated), polylysine conjugates, gramacidin S, artificial viral envelopes or other such intracellular carriers, as well as direct injection of the gene construct or $CaPO_4$ precipitation carried out *in vivo*. It will be appreciated that because transduction of appropriate target cells represents the critical first step in gene therapy, choice of the particular gene delivery system will depend on such factors as the phenotype of the intended target and the route of administration, e.g. locally or systemically. Moreover, such constructs can be used to deliver antisense expression vectors, e.g., constructs whose transcription product is complementary to at least a portion of the coding sequence of one of the subject CDK4-BP genes.

Another aspect of the present invention concerns recombinant forms of the subject CDK4-binding proteins which have at least one biological activity of a subject CDK4-binding protein, or alternatively, which are antagonists of at least one biological activity of a CDK4-BP of the present invention, including naturally occurring dysfunctional mutants. The term "recombinant protein" refers to a protein of the present invention which is produced by recombinant DNA techniques, wherein generally DNA encoding the subject CDK4-binding protein is inserted into a suitable expression vector which is in turn used to transform a host cell to produce the heterologous protein. Moreover, the phrase "derived from", with respect to a recombinant gene encoding the recombinant CDK4-BP, is meant to include within the meaning of "recombinant protein" those proteins having an amino acid sequence of a native CDK4-binding protein of the present invention, or an amino acid sequence similar thereto, which is generated by mutations including substitutions and deletions (including truncation) of a naturally occurring CDK4-binding protein of an organism. Recombinant proteins preferred by the present invention, comprise amino acid sequences which are at least 60% homologous, more preferably 70% homologous and most preferably 80% homologous with an amino acid sequence shown in any of SEQ ID NOS: 25-48. Polypeptides having an activity of, or which are antagonistic to, the subject CDK4-binding proteins and having at least about 90%, more preferably at least about 95%, and most preferably at least about 98-99% homology with a sequence of either in any of SEQ ID NOS: 25-48 are also within the scope of the invention. Thus, the present invention further pertains to recombinant forms of the subject CDK4-binding proteins which are encoded by genes derived from, e.g., a mammal, and which have amino acid sequences evolutionarily related to a subject CDK4-binding protein of any of SEQ ID NOS: 25-48, e.g., CDK4-binding proteins having amino acid sequences which have arisen naturally (e.g. by allelic variance or by differential

splicing), as well as mutational variants of *cdc37* proteins which are derived, for example, by combinatorial mutagenesis.

The present invention further pertains to methods of producing the subject CDK4-binding proteins. For example, a host cell transfected with a nucleic acid vector directing expression of a nucleotide sequence encoding one of the subject CDK4-binding proteins can be cultured under appropriate conditions to allow expression of the polypeptide to occur. The polypeptide may be secreted and isolated from a mixture of host cells and medium. Alternatively, the polypeptide may be retained cytoplasmically and the cells harvested, lysed and the protein isolated. A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art.

The recombinant CDK4-binding protein can be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins including ion-exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for such polypeptide. In a preferred embodiment, the recombinant CDK4-binding protein is a fusion protein containing a domain which facilitates its purification, such as a CDK4-BP-GST or poly(His)-CDK4-BP fusion protein.

Thus, a nucleotide sequence derived from the cloning of the CDK4-binding proteins of the present invention, encoding all or a selected portion of a protein, can be used to produce a recombinant form of a CDK4-BP via microbial or eukaryotic cellular processes. Ligating the polynucleotide sequence into a gene construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures used in producing other well-known intracellular proteins, e.g. p53, CDK4, RB, p16, p21, and the like. Similar procedures, or modifications thereof, can be employed to prepare recombinant CDK4-binding proteins, or portions thereof, by microbial means or tissue-culture technology in accord with the subject invention.

The recombinant CDK4-BP gene can be produced by ligating a nucleic acid encoding a subject CDK4-binding protein, or a portion thereof, into a vector suitable for expression in either prokaryotic cells, eukaryotic cells, or both. Expression vehicles for production of recombinant forms of the subject CDK4-binding proteins include plasmids and other vectors. For instance, suitable vectors for the expression of a CDK4-BP include plasmids of the types: pBR322-derived plasmids, pEMBL-derived plasmids, pEX-derived plasmids, pBTac-derived plasmids and pUC-derived plasmids for expression in prokaryotic cells, such as *E. coli*. In an illustrative embodiment, a CDK4-binding protein is produced recombinantly utilizing an expression vector generated by sub-cloning a gene encoding the protein from the pJG4-5-

CDKBP library (ATCC accesssion no. 75788) using, for example, primers based on 5' or 3' sequences of the particular pJG4-5 gene (see Table 1) and/or primers based on the flanking plasmid sequences of the pJG4-5 plasmid (e.g. SEQ ID Nos. 71 and 72).

A number of vectors exist for the expression of recombinant proteins in yeast. For instance, YEP24, YIP5, YEP51, YEP52, pYES2, and YRP17 are cloning and expression vehicles useful in the introduction of genetic constructs into *S. cerevisiae* (see, for example, Broach *et al.* (1983) in *Experimental Manipulation of Gene Expression*, ed. M. Inouye Academic Press, p. 83). These vectors can replicate in *E. coli* due the presence of the pBR322 ori, and in *S. cerevisiae* due to the replication determinant of the yeast 2 micron plasmid. In addition, drug resistance markers such as ampicillin can be used.

The preferred mammalian expression vectors contain both prokaryotic sequences to facilitate the propagation of the vector in bacteria, and one or more eukaryotic transcription units that are expressed in eukaryotic cells. The pcDNAI/amp, pcDNAI/neo, pRc/CMV, pSV2gpt, pSV2neo, pSV2-dhfr, pTk2, pRSVneo, pMSG, pSVT7, pko-neo and pHyg derived vectors are examples of mammalian expression vectors suitable for transfection of eukaryotic cells. Some of these vectors are modified with sequences from bacterial plasmids, such as pBR322, to facilitate replication and drug resistance selection in both prokaryotic and eukaryotic cells. Alternatively, derivatives of viruses such as the bovine papilloma virus (BPV-1), or Epstein-Barr virus (pHEBo, pREP-derived and p205) can be used for transient expression of proteins in eukaryotic cells. The various methods employed in the preparation of the plasmids and transformation of host organisms are well known in the art. For other suitable expression systems for both prokaryotic and eukaryotic cells, as well as general recombinant procedures, see *Molecular Cloning: A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press:1989) Chapters 16 and 17. In some instances, it may be desirable to express the recombinant CDK4-binding protein by the use of a baculovirus expression system. Examples of such baculovirus expression systems include pVL-derived vectors (such as pVL1392, pVL1393 and pVL941), pAcUW-derived vectors (such as pAcUW1), and pBlueBac-derived vectors (such as the ß-gal containing pBlueBac III).

When expression of a portion of one of the subject CDK4-binding proteins is desired, i.e. a truncation mutant, it may be necessary to add a start codon (ATG) to the oligonucleotide fragment containing the desired sequence to be expressed. It is well known in the art that a methionine at the N-terminal position can be enzymatically cleaved by the use of the enzyme methionine aminopeptidase (MAP). MAP has been cloned from *E. coli* (Ben-Bassat *et al.* (1987) *J. Bacteriol.* 169:751-757) and *Salmonella typhimurium* and its *in vitro* activity has been demonstrated on recombinant proteins (Miller *et al.* (1987) *PNAS* *84*:2718-1722). Therefore, removal of an N-terminal methionine, if desired, can be achieved

either *in vivo* by expressing CDK4-BP-derived polypeptides in a host which produces MAP (e.g., *E. coli* or CM89 or *S. cerevisiae*), or *in vitro* by use of purified MAP (e.g., procedure of Miller *et al. supra*).

Alternatively, the coding sequences for the polypeptide can be incorporated as a part of a fusion gene including a nucleotide sequence encoding a different polypeptide. This type of expression system can be useful under conditions where it is desirable to produce an immunogenic fragment of a CDK4-binding protein. For example, the VP6 capsid protein of rotavirus can be used as an immunologic carrier protein for portions of the CDK4-BP polypeptide, either in the monomeric form or in the form of a viral particle. The nucleic acid sequence corresponding to a portion of a subject CDK4-binding protein to which antibodies are to be raised can be incorporated into a fusion gene construct which includes coding sequences for a late vaccinia virus structural protein to produce a set of recombinant viruses expressing fusion proteins comprising a portion of the protein CDK4-BP as part of the virion. It has been demonstrated with the use of immunogenic fusion proteins utilizing the Hepatitis B surface antigen fusion proteins that recombinant Hepatitis B virions can be utilized in this role as well. Similarly, chimeric constructs coding for fusion proteins containing a portion of a subject CDK4-binding protein and the poliovirus capsid protein can be created to enhance immunogenicity of the set of polypeptide antigens (see, for example, EP Publication No. 0259149; and Evans *et al.* (1989) *Nature* 339:385; Huang *et al.* (1988) *J. Virol.* 62:3855; and Schlienger *et al.* (1992) *J. Virol.* 66:2).

The Multiple Antigen Peptide system for polypeptide-based immunization can also be utilized to generate an immunogen, wherein a desired portion of a subject CDK4-binding protein is obtained directly from organo-chemical synthesis of the polypeptide onto an oligomeric branching lysine core (see, for example, Posnett *et al.* (1988) *JBC* 263:1719 and Nardelli *et al.* (1992) *J. Immunol.* 148:914). Antigenic determinants of the subject CDK4-binding proteins can also be expressed and presented by bacterial cells.

In addition to utilizing fusion proteins to enhance immunogenicity, it is widely appreciated that fusion proteins can also facilitate the expression of proteins, such as any one of the CDK4-binding proteins of the present invention. For example, a CDK4-binding protein of the present invention can be generated as a glutathione-S-transferase (GST- fusion protein). Such GST fusion proteins can enable easy purification of a CDK4-binding protein, such as by the use of glutathione-derivativized matrices (see, for example, *Current Protocols in Molecular Biology*, eds. Ausabel *et al.* (N.Y.: John Wiley & Sons, 1991)). In another embodiment, a fusion gene coding for a purification leader sequence, such as a poly-(His)/enterokinase cleavage site sequence at the N-terminus of the desired portion of a CDK4-binding protein, can allow purification of the poly(His)- expressed CDK4-BP-fusion protein by affinity chromatography using a Ni^{2+} metal resin. The purification leader

sequence can then be subsequently removed by treatment with enterokinase (e.g., see Hochuli *et al.* (1987) *J. Chromatography* 411:177; and Janknecht *et al. PNAS* 88:8972).

Techniques for making fusion genes are well known. Essentially, the joining of various DNA fragments coding for different polypeptide sequences is performed in accordance with conventional techniques, employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992).

The present invention also makes available isolated CDK4-binding proteins which are isolated from, or otherwise substantially free of other cellular or viral proteins normally associated with the protein, e.g. other cell-cycle proteins, e.g. CDKs, cyclins, p16, p21, p19 or PCNA. The term "substantially free of other cellular or viral proteins" (also referred to herein as "contaminating proteins") is defined as encompassing CDK4-BP preparations comprising less than 20% (by dry weight) contaminating protein, and preferably comprises less than 5% contaminating protein. Functional forms of the subject CDK4-binding proteins can be prepared, for the first time, as purified preparations by using, for example, a cloned gene as described herein. By "purified", it is meant, when referring to a polypeptide or DNA or RNA sequence, that the indicated molecule is present in the substantial absence of other biological macromolecules, such as other proteins (e.g. other CDK4-BPs, or CDKs). The term "purified" as used herein preferably means at least 80% by dry weight, more preferably in the range of 95-99% by weight, and most preferably at least 99.8% by weight, of biological macromolecules of the same type present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 5000, can be present). The term "pure" as used herein preferably has the same numerical limits as "purified" immediately above. "Isolated" and "purified" do not encompass either natural materials in their native state or natural materials that have been separated into components (e.g., in an acrylamide gel) but not obtained either as pure (e.g. lacking contaminating proteins, or chromatography reagents such as denaturing agents and polymers, e.g. acrylamide or agarose) substances or solutions. The term polypeptide, as used herein, refers to peptides, proteins, and polypeptides.

However, the subject polypeptides can also be provided in pharmaceutically acceptable carriers for formulated for a variety of modes of administration, including

systemic and topical or localized administration. Techniques and formulations generally may be found in Remmington's Pharmaceutical Sciences, Meade Publishing Co., Easton, PA. In an exemplary embodiment, the polypeptide is provided for transmucosal or transdermal delivery. For such administration, penetrants appropriate to the barrier to be permeated are used in the formulation with the polypeptide. Such penetrants are generally known in the art, and include, for example, for transmucosal administration bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration may be through nasal sprays or using suppositories. For topical administration, the oligomers of the invention are formulated into ointments, salves, gels, or creams as generally known in the art.

Another aspect of the invention related to polypeptides derived from the full-length CDK4-binding protein. Isolated peptidyl portions of the subject proteins can be obtained by screening polypeptides recombinantly produced from the corresponding fragment of the nucleic acid encoding such polypeptides. In addition, fragments can be chemically synthesized using techniques known in the art such as conventional Merrifield solid phase f-Moc or t-Boc chemistry. For example, the protein can be arbitrarily divided into fragments of desired length with no overlap of the fragments, or preferably divided into overlapping fragments of a desired length. The fragments can be produced (recombinantly or by chemical synthesis) and tested to identify those peptidyl fragments which can function as either agonists or antagonists of, for example, CDK4 activation, such as by microinjection assays. In an illustrative embodiment, peptidyl portions of *cdc37* can tested for CDK-binding activity or *erk*-binding, as well as inhibitory ability, by expression as, for example, thioredoxin fusion proteins, each of which contains a discrete fragment of the protein (see, for example, U.S. Patents 5,270,181 and 5,292,646; and PCT publication WO94/ 02502).

It is also possible to modify the structure of the subject CDK4-binding proteins for such purposes as enhancing therapeutic or prophylactic efficacy, or stability (e.g., *ex vivo* shelf life and resistance to proteolytic degradation *in vivo*). Such modified polypeptides, when designed to retain at least one activity of the naturally-occurring form of the protein, are considered functional equivalents of the CDK4-binding proteins described in more detail herein. Such modified polypeptides can be produced, for instance, by amino acid substitution, deletion, or addition.

Moreover, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid (i.e. conservative mutations) will not have a major effect on the biological activity of the resulting molecule. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids are can be divided into four

families: (1) acidic = aspartate, glutamate; (2) basic = lysine, arginine, histidine; (3) nonpolar = alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar = glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. In similar fashion, the amino acid repertoire can be grouped as (1) acidic = aspartate, glutamate; (2) basic = lysine, arginine histidine, (3) aliphatic = glycine, alanine, valine, leucine, isoleucine, serine, threonine, with serine and threonine optionally be grouped separately as aliphatic-hydroxyl; (4) aromatic = phenylalanine, tyrosine, tryptophan; (5) amide = asparagine, glutamine; and (6) sulfur -containing = cysteine and methionine. (see, for example, *Biochemistry*, 2nd ed, Ed. by L. Stryer, WH Freeman and Co.:1981). Whether a change in the amino acid sequence of a polypeptide results in a functional CDK4-BP homolog can be readily determined by assessing the ability of the variant polypeptide to produce a response in cells in a fashion similar to the wild-type CDK4-BP. Peptides in which more than one replacement has taken place can readily be tested in the same manner.

This invention further contemplates a method of generating sets of combinatorial mutants of any one of the presently disclosed CDK4-binding proteins, as well as truncation mutants, and is especially useful for identifying potentially useful variant sequences which are useful in regulating cell growth of differentiation. One purpose for screening such combinatorial libraries is, for example, to isolate novel CDK4-BP homologs which function i the capacity of one of either an agonists or an antagonist of the biological activities of the wild-type ("authentic") protein, or alternatively, which possess novel activities all together. To illustrate, homologs of the clone #225 kinase can be engineered by the present method to provide catalytically inactive enzymes which maintain binding to CDK4 but which act antagonistically to the role of the native kinase in eukaryotic cells, e.g. in regulating cell growth, e.g. in regulating paracrine signal transduction. Similar embodiments are contemplated for *cdc37* polypeptides which retain the ability to bind to an *erk* kinase, e.g. *erk1* or *erk2*. Such proteins, when expressed from recombinant DNA constructs, can be used in gene therapy protocols.

Likewise, mutagenesis can give rise to CDK4-BP homologs which have intracellular half-lives dramatically different than the corresponding wild-type protein. For example, the altered protein can be rendered either more stable or less stable to proteolytic degradation or other cellular process which result in destruction of, or otherwise inactivation of, the authentic CDK4-binding protein. Such CDK4-BP homologs, and the genes which encode them, can be utilized to alter the envelope of expression for the particular recombinant CDK4 binding proteins by modulating the half-life of the recombinant protein. For instance, a short half-life can give rise to more transient biological effects associated with a particular recombinant CDK4-binding protein and, when part of an inducible expression system, can

allow tighter control of recombinant CDK4-BP levels within the cell. As above, such proteins, and particularly their recombinant nucleic acid constructs, can be used in gene therapy protocols.

In a representative embodiment of this method, the amino acid sequences for a population of *cdc37* protein homologs are aligned, preferably to promote the highest homology possible. Such a population of variants can include, for example, homologs from one or more species, or homologs from the same species but which differ due to mutation. Amino acids which appear at each position of the aligned sequences are selected to create a degenerate set of combinatorial sequences. In a preferred embodiment, the combinatorial library is produced by way of a degenerate library of genes encoding a library of polypeptides which each include at least a portion of potential *cdc37* protein sequences. For instance, a mixture of synthetic oligonucleotides can be enzymatically ligated into gene sequences such that the degenerate set of potential *cdc37* nucleotide sequences are expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g. for phage display).

There are many ways by which the library of potential homologs can be generated from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be carried out in an automatic DNA synthesizer, and the synthetic genes then be ligated into an appropriate gene for expression. The purpose of a degenerate set of genes is to provide, in one mixture, all of the sequences encoding the desired set of potential *cdc37* sequences. The synthesis of degenerate oligonucleotides is well known in the art (see for example, Narang, SA (1983) Tetrahedron 39:3; Itakura et al. (1981) Recombinant DNA, Proc. 3rd Cleveland Sympos. Macromolecules, ed. AG Walton, Amsterdam: Elsevier pp273-289; Itakura et al. (1984) Annu. Rev. Biochem. 53:323; Itakura et al. (1984) Science 198:1056; Ike et al. (1983) Nucleic Acid Res. 11:477. Such techniques have been employed in the directed evolution of other proteins (see, for example, Scott et al. (1990) Science 249:386-390; Roberts et al. (1992) PNAS 89:2429-2433; Devlin et al. (1990) Science 249: 404-406; Cwirla et al. (1990) PNAS 87: 6378-6382; as well as U.S. Patents No: 5,223,409, 5,198,346, and 5,096,815).

Alternatively, other forms of mutagenesis can be utilized to generate a combinatorial library. For example, CDK4-BP homologs (both agonist and antagonist forms) can be generated and isolated from a library by screening using, for example, alanine scanning mutagenesis and the like (Ruf et al. (1994) Biochemistry 33:1565-1572; Wang et al. (1994) J. Biol. Chem. 269:3095-3099; Balint et al. (1993) Gene 137:109-118; Grodberg et al. (1993) Eur. J. Biochem. 218:597-601; Nagashima et al. (1993) J. Biol. Chem. 268:2888-2892; Lowman et al. (1991) Biochemistry 30:10832-10838; and Cunningham et al. (1989) Science 244:1081-1085), by linker scanning mutagenesis (Gustin et al. (1993) Virology 193:653-660; Brown et al. (1992) Mol. Cell Biol. 12:2644-2652; McKnight et al. (1982) Science 232:316);

by saturation mutagenesis (Meyers et al. (1986) Science 232:613); by PCR mutagenesis (Leung et al. (1989) Method Cell Mol Biol 1:11-19); or by random mutagenesis (Miller et al. (1992) A Short Course in Bacterial Genetics, CSHL Press, Cold Spring Harbor, NY; and Greener et al. (1994) Strategies in Mol Biol 7:32-34). Linker scanning matagenesis, particularly in a combinatorial setting, is on attractive method for identifying truncated (bioactive) forms of the protein.

A wide range of techniques are known in the art for screening gene products of combinatorial libraries made by point mutations and truncations, and, for that matter, for screening cDNA libraries for gene products having a certain property. Such techniques will be generally adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of CDK4-BP homologs. The most widely used techniques for screening large gene libraries typically comprises cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates relatively easy isolation of the vector encoding the gene whose product was detected. Each of the illustrative assays described below are amenable to high through-put analysis as necessary to screen large numbers of degenerate sequences created by combinatorial mutagenesis techniques.

In an illustrative embodiment of a screening assay, the candidate combinatorial gene products are displayed on the surface of a cell, and the ability of particular cells or viral particles to bind a CDK, such as CDK4 or CDK6, or other binding partners of that CDK4-binding protein, via this gene product is detected in a "panning assay". For instance, the gene library can be cloned into the gene for a surface membrane protein of a bacterial cell (Ladner et al., WO 88/06630; Fuchs et al. (1991) Bio/Technology 9:1370-1371; and Goward et al. (1992) TIBS 18:136-140), and the resulting fusion protein detected by panning, e.g. using a fluorescently labeled molecule which binds the CDK4-binding protein, e.g. FITC-CDK4, to score for potentially functional homologs. Cells can be visually inspected and separated under a fluorescence microscope, or, where the morphology of the cell permits, separated by a fluorescence-activated cell sorter.

In similar fashion, the gene library can be expressed as a fusion protein on the surface of a viral particle. For instance, in the filamentous phage system, foreign peptide sequences can be expressed on the surface of infectious phage, thereby conferring two significant benefits. First, since these phage can be applied to affinity matrices at very high concentrations, a large number of phage can be screened at one time. Second, since each infectious phage displays the combinatorial gene product on its surface, if a particular phage is recovered from an affinity matrix in low yield, the phage can be amplified by another round of infection. The group of almost identical E. coli filamentous phages M13, fd, and fl

are most often used in phage display libraries, as either of the phage gIII or gVIII coat proteins can be used to generate fusion proteins without disrupting the ultimate packaging of the viral particle (Ladner et al. PCT publication WO 90/02909; Garrard et al., PCT publication WO 92/09690; Marks et al. (1992) J. Biol. Chem. 267:16007-16010; Griffiths et al. (1993) EMBO J 12:725-734; Clackson et al. (1991) Nature 352:624-628; and Barbas et al. (1992) PNAS 89:4457-4461).

In an illustrative embodiment, the recombinant phage antibody system (RPAS, Pharmacia Catalog number 27-9400-01) can be easily modified for use in expressing and screening CDK4-binding protein combinatorial libraries of the present invention. For instance, the pCANTAB 5 phagemid of the RPAS kit contains the gene which encodes the phage gIII coat protein. The combinatorial gene library can be cloned into the phagemid adjacent to the gIII signal sequence such that it will be expressed as a gIII fusion protein. After ligation, the phagemid is used to transform competent E. coli TG1 cells. Transformed cells are subsequently infected with M13KO7 helper phage to rescue the phagemid and its candidate gene insert. The resulting recombinant phage contain phagemid DNA encoding a specific candidate CDK4-binding protein, and display one or more copies of the corresponding fusion coat protein. The phage-displayed candidate proteins which are capable of, for example, binding CDK4, are selected or enriched by panning. For instance, the phage library can be panned on glutathione immobilized CDK4-GST fusion proteins, and unbound phage washed away from the cells. The bound phage is then isolated, and if the recombinant phage express at least one copy of the wild type gIII coat protein, they will retain their ability to infect E. coli. Thus, successive rounds of reinfection of E. coli, and panning will greatly enrich for homologs which can then be screened for further biological activities in order to differentiate agonists and antagonists.

Consequently, the invention also provides for reduction of the subject CDK4-binding proteins to generate mimetics, e.g. peptide or non-peptide agents, which are able to mimic binding of the authentic protein to another cellular partner, e.g. a cyclin-dependent kinase, e.g. CDK4, or other cellular protein, e.g., an *erk* kinase, p53 or Src, etc. Such mutagenic techniques as described above, as well as the thioredoxin system, are also particularly useful for mapping the determinants of a CDK4-binding protein which participate in protein-protein interactions involved in, for example, binding of the subject protein to CDK4, CDK6 etc. To illustrate, the critical residues of a CDK4-binding protein which are involved in molecular recognition of CDK4 can be determined and used to generate peptidomimetics which bind to CDK4, and by inhibiting binding of the CDK4-binding protein, act to prevent activation of the kinase. By employing, for example, scanning mutagenesis to map the amino acid residues of the CDK4-binding protein which are involved in binding CDK4, peptidomimetic compounds (e.g. diazepine or isoquinoline derivatives) can be generated which mimic those

residues in binding to the kinase. For instance, non-hydrolyzable peptide analogs of such residues can be generated using benzodiazepine (e.g., see Freidinger et al. in Peptides: Chemistry and Biology, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al. in Peptides: Chemistry and Biology, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted gama lactam rings (Garvey et al. in Peptides: Chemistry and Biology, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al. (1986) J. Med. Chem. 29:295; and Ewenson et al. in Peptides: Structure and Function (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, IL, 1985), β-turn dipeptide cores (Nagai et al. (1985) Tetrahedron Lett 26:647; and Sato et al. (1986) J Chem Soc Perkin Trans 1:1231), and β-aminoalcohols (Gordon et al. (1985) Biochem Biophys Res Commun 126:419; and Dann et al. (1986) Biochem Biophys Res Commun 134:71).

Another aspect of the invention pertains to an antibody specifically reactive with one of the subject CDK4-binding proteins. For example, by using immunogens derived from the present activity CDK4-binding proteins, based on the cDNA sequences, anti-protein/anti-peptide antisera or monoclonal antibodies can be made by standard protocols (See, for example, *Antibodies: A Laboratory Manual* ed. by Harlow and Lane (Cold Spring Harbor Press: 1988)). A mammal such as a mouse, a hamster or a rabbit can be immunized with an immunogenic form of the polypeptide (e.g., CDK4-binding protein or an antigenic fragment which is capable of eliciting an antibody response). Techniques for conferring immunogenicity on a protein or polypeptide include conjugation to carriers or other techniques well known in the art. An immunogenic portion of the subject CDK4-binding proteins can be administered in the presence of adjuvant. The progress of immunization can be monitored by detection of antibody titers in plasma or serum. Standard ELISA or other immunoassays can be used with the immunogen as antigen to assess the levels of antibodies. In a preferred embodiment, the subject antibodies are immunospecific for antigenic determinants of the CDK4-binding proteins of the present invention, e.g. antigenic determinants of a protein represented by one of SEQ ID NOS: 25-48 or a closely related human or non-human mammalian homolog (e.g. 90 percent homologous, more preferably at least 95 percent homologous). In yet a further preferred embodiment of the present invention, the anti-CDK4-BP antibodies do not substantially cross react (i.e. react specifically) with a protein which is: e.g. less than 90 percent homologous to one of SEQ ID NOS: 25-48; e.g. less than 95 percent homologous with one of SEQ ID NOS: 25-48; e.g. less than 98-99 percent homologous with one of SEQ ID NOS: 25-48. By "not substantially cross react", it is meant that the antibody has a binding affinity for a nonhomologous protein (e.g. CDK4) which is less than 10 percent, more preferably less than 5 percent, and even more preferably less than 1 percent, of the binding affinity of that antibody for a protein of SEQ ID NOS: 25-48.

Following immunization, anti-CDK4-BP antisera can be obtained and, if desired, polyclonal anti-CDK4-BP antibodies isolated from the serum. To produce monoclonal antibodies, antibody producing cells (lymphocytes) can be harvested from an immunized animal and fused by standard somatic cell fusion procedures with immortalizing cells such as myeloma cells to yield hybridoma cells. Such techniques are well known in the art, and include, for example, the hybridoma technique (originally developed by Kohler and Milstein, (1975) *Nature*, 256: 495-497), the human B cell hybridoma technique (Kozbar *et al.*, (1983) *Immunology Today*, 4: 72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole *et al.*, (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. pp. 77-96). Hybridoma cells can be screened immunochemically for production of antibodies specifically reactive with a CDK4-binding protein of the present invention and monoclonal antibodies isolated from a culture comprising such hybridoma cells.

The term antibody as used herein is intended to include fragments thereof which are also specifically reactive with one of the subject CDK4-binding protein. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, $F(ab')_2$ fragments can be generated by treating antibody with pepsin. The resulting $F(ab')_2$ fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules having an anti-CDK4-BP portion.

Both monoclonal and polyclonal antibodies (Ab) directed against the subject CDK4-BP or CDK4-BP variants, and antibody fragments such as Fab` and $F(ab`)_2$, can be used to block the action of a subject CDK4-BP and allow the study of the role of a particular CDK4 binding protein of the present invention in the normal cellular function of the subject CDK4-binding protein, e.g. by microinjection of anti-CDK4BP antibodies of the present invention.

Antibodies which specifically bind CDK4-BP epitopes can also be used in immunohistochemical staining of tissue samples in order to evaluate the abundance and pattern of expression of each of the subject CDK4-binding protein. Anti-CDK4-BP antibodies can be used diagnostically in immuno-precipitation and immuno-blotting to detect and evaluate CDK4-BP levels in tissue or bodily fluid as part of a clinical testing procedure. Likewise, the ability to monitor CDK4-BP levels in an individual can allow determination of the efficacy of a given treatment regimen for an individual afflicted with a disorder. The level of CDK4-BP can be measured in cells found in bodily fluid, such as in samples of cerebral spinal fluid, or can be measured in tissue, such as produced by biopsy. Diagnostic assays using anti-CDK4-BP antibodies can include, for example, immunoassays designed to aid in early diagnosis of a neoplastic or hyperplastic disorder, e.g. the presence of cancerous cells in the sample, e.g. to detect cells in which a lesion of the CDK4-BP gene has occurred.

Another application of anti-CDK4-BP antibodies is in the immunological screening of cDNA libraries constructed in expression vectors such as λgt11, λgt18-23, λZAP, and λ ORF8. Messenger libraries of this type, having coding sequences inserted in the correct reading frame and orientation, can produce fusion proteins. For instance, λgt11 will produce fusion proteins whose amino termini consist of ß-galactosidase amino acid sequences and whose carboxy termini consist of a foreign polypeptide. Antigenic epitopes of a subject CDK4-BP can then be detected with antibodies, as, for example, reacting nitrocellulose filters lifted from infected plates with anti-CDK4-BP antibodies. Phage, scored by this assay, can then be isolated from the infected plate. Thus, the presence of CDK4-BP homologs can be detected and cloned from other sources, and alternate isoforms (including splicing variants) can be detected and cloned from human sources.

Antibodies which are specifically immunoreactive with a CDK4-binding protein of the present invention can also be used in immunohistochemical staining of tissue samples in order to evaluate the abundance and pattern of expression of the protein. Such antibodies can be used diagnostically in immuno-precipitation and immuno-blotting to detect and evaluate levels of one or more CDK4-binding proteins in tissue or cells isolated from a bodily fluid as part of a clinical testing procedure. For instance, such measurements can be useful in predictive valuations of the onset or progression of tumors. Likewise, the ability to monitor certain CDK4-binding protein levels in an individual can allow determination of the efficacy of a given treatment regimen for an individual afflicted with such a disorder. Diagnostic assays using the subject antibodies, can include, for example, immunoassays designed to aid in early diagnosis of a neoplastic or hyperplastic disorder, e.g. the presence of cancerous cells in the sample, e.g. to detect cells in which alterations in expression levels of a CDK4-BP gene has occurred relative to normal cells.

In addition, nucleotide probes can be generated from the cloned sequence of the CDK4-BP genes, which probes will allow for histological screening of intact tissue and tissue samples for the presence of a CDK4-BP-encoding mRNA. Similar to the diagnostic uses of the subject antibodies, the use of probes directed to CDK4-BP messages, or to genomic CDK4-BP gene sequences, can be used for both predictive and therapeutic evaluation of allelic mutations or abnormal transcription which might be manifest in, for example, neoplastic or hyperplastic disorders (e.g. unwanted cell growth).

Accordingly, the present method provides a method for determining if a subject is at risk for a disorder characterized by unwanted cell proliferation. In preferred embodiments, the method can be generally characterized as comprising detection, in a tissue of the subject, the presence or absence of a genetic lesion manifest as at least one of (i) a mutation of a gene encoding a CDK4-binding protein, or (ii) the mis-expression of that gene. To illustrate, such genetic lesions can be detected by ascertaining the existence of at least one of (i) a deletion of

one or more nucleotides from a gene, (ii) an addition of one or more nucleotides to a gene, (iii) a substitution of one or more nucleotides of a gene, (iv) a gross chromosomal rearrangement of a gene, (v) a gross alteration in the level of a messenger RNA transcript of a gene, (vi) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a gene, and (vii) a non-wild type level of a CDK4-binding protein. In one aspect of the invention, there is provided a probe/primer comprising an oligonucleotide containing a region of nucleotide sequence which is capable of hybridizing to a sense or antisense sequence of one of SEQ. ID Nos: 1-24, or naturally occurring mutants thereof, or 5' or 3' flanking sequences or intronic sequences naturally associated with the subject CDK4-BP gene or naturally occurring mutants thereof. The probe is exposed to nucleic acid of a tissue sample; and the hybridization of the probe to the sample nucleic acid is detected. In certain embodiments, detection of the lesion comprises utilizing the probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Patent Nos. 4,683,195 and 4,683,202), or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) *Science* 241:1077-1080; and Nakazawa et al. (1944) *PNAS* 91:360-364), the later of which can be particularly useful for detecting point mutations in the gene. Alternatively, the level of a CDK4-binding protein can detected in an immunoassay.

As set out above, the present invention also provides assays for identifying drugs which are either agonists or antagonists of the normal cellular function of a CDK4-binding protein, or of the role of that protein in the pathogenesis of normal or abnormal cellular proliferation and/or differentiation and disorders related thereto, as mediated by, for example binding of the CDK4-binding protein to a target protein, e.g., CDK4, CDK6, or another cellular protein. In one embodiment, the assay evaluates the ability of a compound to modulate binding of a CDK4-binding protein to a CDK or other of cell-cycle regulatory protein. While the following description is directed generally to embodiments exploiting the interaction between a CDK4-binding protein, *cdc37*, and a CDK, it will be understood that these examples are merely illustrative, and that similar embodiments can be generated using, for example, a *erk* polypeptide, such as *erk1* or *erk2*, as target proteins for *cdc37*. Moreover, the other CDK4-binding proteins of the present invention can be exploited in similar assays.

A variety of assay formats will suffice and, in light of the present disclosure, those not expressly described herein will nevertheless be comprehended by one of ordinary skill in the art. Agents to be tested for their ability to act as *cdc37* inhibitors can be produced, for example, by bacteria, yeast or other organisms (e.g. natural products), produced chemically (e.g. small molecules, including peptidomimetics), or produced recombinantly. In a preferred embodiment, the test agent is a small organic molecule, e.g., other than a peptide, oligonucleotide, or analog thereof, having a molecular weight of less than about 2,000 daltons.

In many drug screening programs which test libraries of compounds and natural extracts, high throughput assays are desirable in order to maximize the number of compounds surveyed in a given period of time. Assays which are performed in cell-free systems, such as may be derived with purified or semi-purified proteins, are often preferred as "primary" screens in that they can be generated to permit rapid development and relatively easy detection of an alteration in a molecular target which is mediated by a test compound. Moreover, the effects of cellular toxicity and/or bioavailability of the test compound can be generally ignored in the *in vitro* system, the assay instead being focused primarily on the effect of the drug on the molecular target as may be manifest in an alteration of binding affinity between *cdc37* and other proteins, or in changes in a property of the molecular target for *cdc37* binding. Accordingly, in an exemplary screening assay of the present invention, the compound of interest is contacted with an isolated and purified *cdc37* polypeptide which is ordinarily capable of binding CDK4. To the mixture of the compound and *cdc37* polypeptide is then added a composition containing a CDK4 polypeptide. Detection and quantification of CDK4/*cdc37* complexes provides a means for determining the compound's efficacy at inhibiting (or potentiating) complex formation between the CDK4 and *cdc37* polypeptides. The efficacy of the compound can be assessed by generating dose response curves from data obtained using various concentrations of the test compound. Moreover, a control assay can also be performed to provide a baseline for comparison. In the control assay, isolated and purified CDK4 is added to a composition containing the *cdc37* protein, and the formation of CDK4/*cdc37* complex is quantitated in the absence of the test compound. It will be understood that, in general, the order in which the reactants may be admixed can be varied, and can be admixed simultaneously. Moreover, CDK4 can be substituted with other proteins to which *cdc37* binds, as a complex by immunoprecipitation of *cdc37* by anti-*cdc37* antibodies, such as a protein having a molecular weight of approximately 40kd, 42kd, 95kd, 107kd and 117kd.

Complex formation between the *cdc37* polypeptide and target polypeptide may be detected by a variety of techniques. For instance, modulation of the formation of complexes can be quantitated using, for example, detectably labelled proteins such as radiolabelled (e.g. ^{32}P, ^{35}S, ^{14}C or ^{3}H), fluorescently labelled (e.g. FITC), or enzymatically labelled *cdc37* or CDK4 polypeptides, by immunoassay, or by chromatographic detection. The use of enzymatically labeled CDK4 will, of course, generally be used only when enzymatically inactive portions of CDK4 are used, as each protein can possess a measurable intrinsic activity which can be detected.

Typically, it will be desirable to immobilize either the *cdc37* or the CDK4 polypeptide to facilitate separation of *cdc37*/CDK4 complexes from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of

CDK4 to *cdc37*, in the presence and absence of a candidate agent, can be accomplished in any vessel suitable for containing the reactants. Examples include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows the protein to be bound to a matrix. For example, glutathione-S-transferase/*cdc37* (GST/*cdc37*) fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the CDK4 polypeptide, e.g. an ^{35}S-labeled CDK4 polypeptide, and the test compound, and the mixture incubated under conditions conducive to complex formation, e.g. at physiological conditions for salt and pH, though slightly more stringent conditions may be desired, e.g., at 4°C in a buffer containing 0.6M NaCl or a detergent such as 0.1% Triton X-100. Following incubation, the beads are washed to remove any unbound CDK4 polypeptide, and the matrix immobilized radiolabel determined directly (e.g. beads placed in scintilant), or in the supernatant after the *cdc37*/CDK4 complexes are subsequently dissociated. Alternatively, the complexes can dissociated from the matrix, separated by SDS-PAGE, and the level of CDK4 polypeptide found in the bead fraction quantitated from the gel using standard electrophoretic techniques such as described in the appended examples.

Other techniques for immobilizing proteins on matrices are also available for use in the subject assay. For instance, either of the *cdc37* or CDK4 proteins can be immobilized utilizing conjugation of biotin and streptavidin. For instance, biotinylated *cdc37* molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with the *cdc37* but which do not interfere with CDK4 binding can be derivatized to the wells of the plate, and the *cdc37* trapped in the wells by antibody conjugation. As above, preparations of a CDK4 polypeptide and a test compound are incubated in the *cdc37*-presenting wells of the plate, and the amount of *cdc37*/CDK4 complex trapped in the well can be quantitated. Exemplary methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the CDK4 polypeptide, or which are reactive with the *cdc37* protein and compete for binding with the CDK4 polypeptide; as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the CDK4 polypeptide, either intrinsic or extrinisic activity. In the instance of the latter, the enzyme can be chemically conjugated or provided as a fusion protein with a CDK4 polypeptide. To illustrate, the CDK4 polypeptide can be chemically cross-linked or genetically fused with horseradish peroxidase, and the amount of CDK4 polypeptide trapped in the complex can be assessed with a chromogenic substrate of the enzyme, e.g. 3,3'-diamino-benzadine terahydrochloride or 4-chloro-1-napthol. Likewise, a fusion protein comprising the CDK4

polypeptide and glutathione-S-transferase can be provided, and complex formation quantitated by detecting the GST activity using 1-chloro-2,4-dinitrobenzene (Habig et al (1974) *J Biol Chem* 249:7130). Direct detection of the kinase activity of CDK4 can be provided using substrates known in the art, e.g., histone H1.

For processes which rely on immunodetection for quantitating one of the proteins trapped in the complex, antibodies against the protein, such as either anti-CDK4 or anti-*cdc37* antibodies, can be used. Alternatively, the protein to be detected in the complex can be "epitope tagged" in the form of a fusion protein which includes, in addition to the CDK4 polypeptide or *cdc37* sequence, a second polypeptide for which antibodies are readily available (e.g. from commercial sources). For instance, the GST fusion proteins described above can also be used for quantification of binding using antibodies against the GST moiety. Other useful epitope tags include myc-epitopes (e.g., see Ellison et al. (1991) *J Biol Chem* 266:21150-21157) which includes a 10-residue sequence from c-myc, as well as the pFLAG system (International Biotechnologies, Inc.) or the pEZZ-protein A system (Pharamacia, NJ).

Moreover, the subject *cdc37* polypeptides can be used to generate an interaction trap assay, as described in the examples below (see also, U.S. Patent No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J Biol Chem* 268:12046-12054; Bartel et al. (1993) *Biotechniques* 14:920-924; and Iwabuchi et al. (1993) *Oncogene* 8:1693-1696), for subsequently detecting agents which disrupt binding of *cdc37* to a CDK or other cell-cycle regulatory protein, e.g. Src or p53.

The interaction trap assay relies on reconstituting *in vivo* a functional transcriptional activator protein from two separate fusion proteins, one of which comprises the DNA-binding domain of a transcriptional activator fused to a CDK, such as CDK4. The second fusion protein comprises a transcriptional activation domain (e.g. able to initiate RNA polymerase transcription) fused to a *cdc37* polypeptide. When the CDK4 and *cdc37* domains of each fusion protein interact, the two domains of the transcriptional activator protein are brought into sufficient proximity as to cause transcription of a reporter gene. By detecting the level of transcription of the reporter, the ability of a test agent to inhibit (or potentiate) binding of *cdc37* to CDK4 can be evaluated.

In an illustrative embodiment, *Saccharomyces cerevisiae* YPB2 cells are transformed simultaneously with a plasmid encoding a GAL4db-CDK4 fusion and with a plasmid encoding the GAL4ad domain fused to a *cdc37*. Moreover, the strain is transformed such that the GAL4-responsive promoter drives expression of a phenotypic marker. For example, the ability to grow in the absence of histidine can depends on the expression of the HIS3 gene. When the HIS3 gene is placed under the control of a GAL4-responsive promoter, relief of this auxotrophic phenotype indicates that a functional GAL4 activator has been

reconstituted through the interaction of CDK4 and the *cdc37*. Thus, a test agent able to inhibit *cdc37* interaction with CDK4 will result in yeast cells unable to growth in the absence of histidine. Alternatively, the phenotypic marker (e.g. instead of the HIS3 gene) can be one which provides a negative selection (e.g., are cytotoxic) when expressed such that agents which disrupt CDK4/*cdc37* interactions confer positive growth selection to the cells.

In yet another embodiment, a mammalian *cdc37* gene can be used to rescue a yeast cell having a defective Cdc37 gene, such as the temperature sensitive mutant (Cdc37^{TS}; see Reed (1980) *Genetics* 95:561-577; and Reed et al. (1985) *CSH Symp Quant Biol* 50:627-634). For example, a humanized yeast can be generated by amplifying the coding sequence of the human *cdc37* clone, and subcloning this sequence into a vector which contains the yeast *GAL* promoter and *ACT1* termination sequences flanking the *cdc37* coding sequences. This plasmid can then be used to transform a Cdc37^{TS} mutant (Gietz et al. (1992) *Nuc Acid Res* 20:1425). To assay growth rates, cultures of the transformed cells can be grown at 37°C (an impermissive temperature for the TS mutant) in media supplemented with galactose. Turbidity measurements, for example, can be used to easily determine the growth rate. At the non-permissive temperature, growth of the yeast cells becomes dependent upon expression of the human *cdc37* protein. Accordingly, the humanized yeast cells can be utilized to identify compounds which inhibit the action of the human *cdc37* protein. It is also deemed to be within the scope of this invention that the humanized yeast cells of the present assay can be generated so as to comprise other human cell-cycle proteins. For example, human CDKs and human cyclins can also be expressed in the yeast cell. To illustrate, a triple cln deletion mutant of *S. Cerevisae* which is also conditionally deficient in cdc28 (the budding yeast equivalent of cdc2) can be rescued by the co-expression of a human cyclin D1 and human CDK4, demonstrating that yeast cell-cycle machinery can be at least in part replaced with corresponding human regulatory proteins. Roberts et al. (1993) *PCT Publication Number WO 93/06123*. In this manner, the reagent cells of the present assay can be generated to more closely approximate the natural interactions which the mammalian *cdc37* protein might experience.

Furthermore, it will be possible to perform such assays as differential screening assays, which permit comparison of the effects of a drug on a number of different complexes formed between the CDK4-binding protein and other cell-cycle regulatory proteins, e.g. other CDKs. For instance, each of the above assays can be run with a subject CDK4-BP and each of CDK4, CDK5 and CDK6. In side-by-side comparison, therefore, agents can be chosen which selectively effect the formation of, for example, the CDK-BP/CDK4 complex without substantially interferring with the other CDK complexes.

Moreover, certain formats of the subject assays can be used to identify drugs which inhibit proliferation of yeast cells or other lower eukaryotes, but which have a substantially

reduced effect on mammalian cells, thereby improving therapeutic index of the drug as an anti-mycotic agent. To illustrate, the identification of such compounds is made possible by the use of differential screening assays which detect and compare drug-mediated disruption of binding between two or more different types of *cdc37*/CDK complexes. Differential screening assays can be used to exploit the difference in drug-mediated disruption of human CDK/*cdc37* complexes and yeast CDC2/Cdc37 complexes in order to identify agents which display a statistically significant increase in specificity for disrupting the yeast complexes relative to the human complexes. Thus, lead compounds which act specifically to inhibit proliferation of pathogens, such as fungus involved in mycotic infections, can be developed. By way of illustration, the present assays can be used to screen for agents which may ultimately be useful for inhibiting at least one fungus implicated in such mycosis as candidiasis, aspergillosis, mucormycosis, blastomycosis, geotrichosis, cryptococcosis, chromoblastomycosis, coccidioidomycosis, conidiosporosis, histoplasmosis, maduromycosis, rhinosporidosis, nocaidiosis, para-actinomycosis, penicilliosis, monoliasis, or sporotrichosis. For example, if the mycotic infection to which treatment is desired is candidiasis, the present assay can comprise comparing the relative effectiveness of a test compound on mediating disruption of a human CDK4/*cdc37* complex with its effectiveness towards disrupting the equivalent complexes formed from genes cloned from yeast selected from the group consisting of *Candida albicans*, *Candida stellatoidea*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida pseudotropicalis*, *Candida quillermondii*, or *Candida rugosa*. Likewise, the present assay can be used to identify anti-fungal agents which may have therapeutic value in the treatment of aspergillosis by making use of an interaction trap assays derived from CDK and Cdc37 genes cloned from yeast such as *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nidulans*, or *Aspergillus terreus*. Where the mycotic infection is mucormycosis, the complexes can be derived from yeast such as *Rhizopus arrhizus*, *Rhizopus oryzae*, *Absidia corymbifera*, *Absidia ramosa*, or *Mucor pusillus*. Sources of other Cdc37-containing complexes for comparison with a human CDK/*cdc37* complex includes the pathogen *Pneumocystis carinii*.

Moreover, inhibitors of the enzymatic activity of any of the subject CDK-binding proteins which are enzymes, e.g. a kinase, e.g. an isopeptidase, e.g. a protease, can be identified using assays derived from measuring the ability of an agent to inhibit catalytic converstion of a substrate by the subject proteins.

In another aspect, the invention features transgenic non-human animals which express a recombinant CDK4-BP gene of the present invention, or which have had one or more of the subject CDK4-BP gene(s), e.g. heterozygous or homozygous, disrupted in at least one of the tissue or cell-types of the animal.

In another aspect, the invention features an animal model for developmental diseases, which has a CDK4-BP allele which is mis-expressed. For example, a mouse can be bred which has a CDK4-BP allele deleted, or in which all or part of one or more CDK4-BP exons are deleted. Such a mouse model can then be used to study disorders arising from mis-expressed CDK4-BP genes.

Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Interaction Trap

A general transcription-based selection for protein-protein interactions was used to isolate cDNA which encode proteins able to bind to CDK4. Development of the "interaction trap assay" or ITS, is described in, for example, Gyuris et al. (1993) *Cell* 75:791-803; Chien et al. (1991) *PNAS* 88:9578-9582; Dalton et al. (1992) *Cell* 68:597-612; Durfee et al. (1993) *Genes Dev* 7:555-569; Vojteck et al. (1993) *Cell* 74:205-214; Fields et al. (1989) *Nature* 340:245-246; and U.S. Patent Serial number 5,283,173). As carried out in the present invention, the interaction trap comprises three different components: a fusion protein that contains the LexA DNA-binding domain and that is known to be transcriptionally inert (the "bait"); reporter genes that have no basal transcription and whose transcriptional regulatory sequences are dependent on binding of LexA; and the proteins encoded by an expression library, which are expressed as chimeras and whose amino termini contrain an activation domain and other useful moieties (the "fish"). Briefly, baits were produced constitutively from a 211 HIS3+ plasmid under the control of the ADH1 promoter and contained the LexA carboxy-terminal oligomerization region. Baits were made in pLexA(1-202)+pl (described in Ruden et al. *Nature* (1991) 350:250-252; and Gyuris et al. *Cell* (1993) 75:791-803) after PCR amplification of the bait coding sequences from the second amino acid to the Stop codon, except for p53 where the bait moiety starts at amino acid 74. Using the PCR primers described in Table I, CDK2 and CDK3 were cloned as EcoR1-BamH1 fragments; CDK4, cyclin D1, cyclin D2, Cyclin E as EcoR1-Sal1 fragments; CDK5, CDK6, Cdi1 as EcoR1-Xho1 fragments; and retinoblastoma (pRb), mutRb(Δ702-737), p53 and cyclin C as BamH1-Sal1 fragments. When EcoR1 is used, there are two amino acid inserted (EF) between the last amino acid of LexA and the bait moieties. BamH1 fusion results in five amino acid insertion (EFPGI) between LexA and the fused protein.

PCR primers:

CDK2:
5'-GGCGGCCGCGAATTCGAGAACTTCCAAAAGGTGGAAAAG-3'
5'-GCGGCCGCGGATCCAGGCTATCAGAGTCGAAGATGGGGTAC-3'

CDK3:
5'-GCGGCCGCGAATTCGAAGCTGGAGGAGCAACCGGGAGC-3'
5'-GCGGCCGCGGATCCTCAATGGCGGAATCGCTGCAGCAC-3'

CDK5:
5'-GCGGCGGCGTCGACCAGAAATACGAGAAACTGGAAAAG-3'
5'-GCGGCGGCGTCGACCGGGGCCTAGGGCGGACAGAAGTC-3'

CDK6:
5'-GCGGCCGCGAATTCGAGAAGGACGGCCTGTGCCGCGCT-3'
5'-GCGGCGGCCTCGAGGAGGCCTCAGGCTGTATTCAGCTC-3'

Cyclin C:
5'-GGCCGGCCGGGATCCTTGTCGCTCCGCGGCTGCTCCGGCTG-3'
5'-GCGGCCGCGTCGACGTTTTAAGATTGGCTGTAGCTAGAG-3'

Cyclin D1:
5'-GGCCGGCCGGAATTCGAACACCAGCTCCTGTGCTGCGAAG-3'
5'-GCGGCCGCGTCGACGCGCCCTCAGATGTCCACGTCCCGC-3'

Cyclin D2:
5'-GCGGCGGCGAATTCGAGCTGCTGTGCCACGAGGTGGAC-3'
5'-GCGGCGGCGAATTCGAGCTGCTGTGCCACGAGGTGGAC-3'

Cyclin E:
5'-GGCCGGCCGGAATTCAAGGAGGACGGCGGCGCGGAGTTC-3'
5'-GCGGCCGCGTCGACGGGTGGTCACGCCATTTCCGGCCCG-3'

Cdi1:
5'-GCGGCCGCGAATTCAAGCCGCCCAGTTCAATACAAACAAG-3'
5'-GCGGCCGCCTCGAGATTCCTTTATCTTGATACAGATCTTG-3'

Rb:
5'-GCGGCCGCGGATCCAGCCGCCCAAAACCCCCCGAAAAACG-3'
5'-GCGGCCGCGAATTCCTCGAGCTCATTTCTCTTCCTTGTTTGAGG-3'

p53:
5'-GCGGCCGCGGATCCAAGCCCCTGCACCAGCAGCTCCTACA-3'
5'-GCGGCCGCGTCGACTCAGTCTGAGTCAGGCCCTTCTGT-3'

Reporters

The LexAop-LEU2 construction replaced the yeast chromosomal LEU2 gene. The other reporter, pRB1840, one of a series of LexAop-GAL1-lacZ genes (Brent et al. (1985) *Cell* 43:729-736; Kamens et al. (1990) *Mol Cell Biol* 10:2840-2847), was carried on a 2μ plasmid. Basal reporter transcription was extremely low, presumably owing both to the removal of the entire upstream activating sequence from both reporters and to the fact that LexA operators introduced into yeast promoters decrease their transcription (Brent and Ptashne (1984) *Nature* 312:612-615). Reporters were chosen to differ in sensitivity. The LEU2 reporter contained three copies of the high affinity LexA-binding site found upstream of *E. coli* colE1, which presumably bind a total of six dimers of the bait. In contrast, the lacZ gene contained a single lower affinity operator that binds a single dimer of the bait. The operators in the LEU2 reporter were closer to the transcription start point than they were in the lacZ reporter. These differences in the number, affinity, and operator position all contribute to that fact that the LEU2 reporter is more sensitive than the lacZ gene.

Expression Vectors and Library

Library proteins were expressed from pJG4-5, a member of a series of expression plasmids designed to be used in the interaction trap and to facilitate analysis of isolated proteins. These plasmids carry the 2μ replicator and the TRP1 marker. pJG4-5, shown in Figure 1, directs the synthesis of fusion proteins. Proteins expressed from this vector possess the following features: galactose-inducible expression so that their synthesis is conditional, an epitope tag to facilitate detection, a nuclear localization signal to maximize intranuclear concentration to increase selection sensitivity, and an activation domain derived from E. coli (Ma and Ptashne (1987) *Cell* 57:113-119), chosen because its activity is not subject to known regulation by yeast proteins and because it is weak enough to avoid toxicity (Gill and Ptashne (1988) *Nature* 334:721-724; Berger et al. (1992) *Cell* 70:251-265) that might restrict the number or type of interacting proteins recovered. We introduced EcoRI-XhoI cDNA-containing fragments, which were generated from a quiescent normal fibroblast line (WI38), into the pJG4-5 plasmid.

CDK4 Interaction Trap

We began with yeast cells which contained LexAop-LEU2 and LexAop-lacZ reporters and the LexA-CDK4 bait. We introduced the WI38 cDNA library (in pJG4-5) into this strain. We recovered a number of transformants on glucose Ura$^-$ His$^-$ Trp$^-$ plates, scraped them, suspended them in approximately 20 ml of 65% glycerol, 10 mM Tris-HCl (pH 7.5), 10 mM $MgCl_2$, and stored the cells in 1 ml aliquots at -80°C. We determined plating efficiency on galactose Ura$^-$ His$^-$ Trp$^-$ after growing 50 μl of cell suspension for 5 hr in 5 ml of YP medium, 2% galactose. For the selection, about 2 x 10^7 galactose-viable cells were plated on four standard circular 10 cm galactose Ura$^-$ His$^-$ Trp$^-$ Leu$^-$ plates after galactose

induction. After 4 days at 30°C, LEU+ colonies appeared and were collected on glucose Ura^- His^- Trp^- master plates and retested on glucose Ura^- His^- Trp^- Leu^-, galactose Ura^- His^- Trp^- Leu^-, glucose X-Gal Ura^- His^- Trp^-, and galactose X-Gal Ura^- His^- Trp^- plates. Of these, plasmid DNAs were rescued from colonies which showed galactose-dependent growth on Leu^- media and galactose-dependent blue color on X-Gal medium (Hoffman and Winston, (1987) *Gene* 57:267-272), introduced into *E. coli* KC8, and transformants collected on Trp^- ampicillin plates.

We classified library plasmids by restriction pattern on 1.8% agarose; 0.5 x Tris-borate-EDTA gels after digestion with EcoRI and Xhol and either AluI or HaeIII. We reintroduced those plasmids from each map class that contained the longest cDNAs into EGY48 derivatives that contained a panel of different baits, e.g. other CDKs, cyclins, p53, Rb, etc. As is evident from inspection of the data for this experiment (see Figure 2), each of the subject CDK4-binding proteins displayed different binding affinities for other cell-cycle regulatory proteins. This finding is significant for a number of reasons. For example, in chosing a particular CDK4 interaction as a therapeutic target for drug design, therapeutic index concerns might cause selection of a CDK4-BP target which interacts primarily with CDK4 and much less with any other CDK. Alternatively, if desired, the ability of a particular CDK4-BP to bind multiple CDKs can be exploited in testing compounds in differential screening assays as described above. Thus, drugs which can alter the binding of, for example, a particular CDK4-BP to CDK4 but which have less effect on the same complexformed with CDK5, will presumably have a better therapeutic index with regard to neuronal side effects than a drug which interferes equally with both.

Furthermore, a deposit of each of these clones as a library of pJG4-5 plasmids (designated "pJG4-5-CDKBP") containing 24 different proteins isolated in the CDK4 interaction trap has been made with the American Type Culture Collection (Rockville, MD) on May 26, 1994, under the terms of the Budapest Treaty. ATCC Accession number 75788 has been assigned to the deposit. The cDNAs were inserted into this vector as EcoR1-Xho1 fragments. The EcoR1 adaptor sequence is 5'-GAATTCTGCGGCCGC-3' and the open reading frame encoding the interacting protein starts with the first G. With this deposit in hand, one of ordinary skill in the art can generate the subject recombinant CDK4-BP genes abd express recombinant forms of the subject CDK4-binding proteins. For instance, each of the CDK4-binding proteins of the present invention can be amplified froim ATCC deposit no. 75788 by PCR using the following primers:

5'-TAC CAG CCT CTT GCT GAG TGG AGA-3' (SEQ ID No. 71)
5'-TAG ACA AGC CGA CAA CCT TGA TTG-3' (SEQ ID No. 72)

Moreover, it will be immediately evident to those skilled in the art that, in light of the guide to the 5' and 3' ends to each of the clones provided in Table 1, each individual clone of the ATCC deposit can be isolated using primers based on the nucleotide sequences provided

by SEQ ID Nos. 1-24 and 49-70, or a combination of such primers and the primers of SEQ ID Nos. 71 and 72.

Isolated clones can be subcloned into expression vectors in order to produce a recombinant protein, or can be used to generate anti-sense constructs, or can be used to generate oligonucleotide probes. In an illustrative embodiment, oligonucleotide probes have been generated using the coding sequences for each of the clones of the subject ATCC deposit, and used in Southern hybridization and *in situ* hybridization assays to detect the pattern and abundance of expression of each of the CDK4-binding proteins.

Moreover, because each member of the ATCC deposit is a plasmid encoding a fusion protein identified from an interaction trap assay, the clone can be utilized directly from the deposit in a similar ITS employed as, for example, a drug screening assay, or alternatively, a mutagenesis assay for mapping CDK4 binding epitopes.

Table 1
Guide to pJG4-5-CDKBP

Clone	Nucleotide	Peptide
11	SEQ ID No. 1	SEQ ID No. 25
13	SEQ ID No. 2	SEQ ID No. 26
22	SEQ ID No. 3	SEQ ID No. 27
36	SEQ ID No. 4 (5') SEQ ID No. 49 (3')	SEQ ID No. 28 (N-terminal)
61	SEQ ID No. 5 (5') SEQ ID No. 50 (3')	SEQ ID No. 29 (N-terminal)
68	SEQ ID No. 6 (5') SEQ ID No. 51 (3')	SEQ ID No. 30 (N-terminal)
71	SEQ ID No. 7 (full length) SEQ ID No. 69 (5') SEQ ID No. 70 (3')	SEQ ID No. 31
75	SEQ ID No. 8 (5') SEQ ID No. 52 (3')	SEQ ID No. 32 (N-terminal)
116	SEQ ID No. 9 (full length) SEQ ID No. 67 (5') SEQ ID No. 68 (3')	SEQ ID No. 33
118	SEQ ID No. 10 (5') SEQ ID No. 55 (3') SEQ ID No. 55 (Internal)	SEQ ID No. 34 (N-terminal)
121	SEQ ID No. 11 (5') SEQ ID No. 56 (3')	SEQ ID No. 35 (N-terminal)
125	SEQ ID No. 12 (5') SEQ ID No. 57 (3')	SEQ ID No. 36 (N-terminal)
127	SEQ ID No. 13	SEQ ID No. 37
166	SEQ ID No. 15	SEQ ID No. 39

190	SEQ ID No. 16 (5') SEQ ID No. 58 (3')	SEQ ID No. 40 (N-terminal)
193	SEQ ID No. 17	SEQ ID No. 41
216	SEQ ID No. 18 (5') SEQ ID No. 59 (3')	SEQ ID No. 42
225	SEQ ID No. 19	SEQ ID No. 43
227	SEQ ID No. 20 (5') SEQ ID No. 61 (3')	SEQ ID No. 44 (N-terminal)
267	SEQ ID No. 21	SEQ ID No. 45
269	SEQ ID No. 22 (5') SEQ ID No. 63 (3')	SEQ ID No. 46 (N-terminal)
295	SEQ ID No. 23 (5') SEQ ID No. 64 (3')	SEQ ID No. 47 (N-terminal)

All of the above-cited references and publications are hereby incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Mitotix, Inc.
(B) STREET: One Kendall Square, Building 600
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: USA
(F) POSTAL CODE (ZIP): 02139
(G) TELEPHONE: (617) 225-0001
(H) TELEFAX: (617) 225-0005

(ii) TITLE OF INVENTION: CDK4-Binding Proteins

(iii) NUMBER OF SEQUENCES: 72

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: ASCII (text)

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/253,155
(B) FILING DATE: 2-JUN-1994

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1638 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCTGCG GCCGCATGGA TACAGATACA GATACATTCA CCTGTCAGAA AGATGGTCGC 60

TGGTTCCCTG AGAGAATCTC CTGCAGTCCT AAAAAATGTC CTCTCCCGGA AAACATAACA 120

CATATACTTG TACATGGGGA CGATTTCAGT GTGAATAGGC AAGTTTCTGT GTCATGTGCA 180

GAAGGGTATA CCTTTGAGGG AGTTAACATA TCAGTATGTC AGCTTGATGG AACCTGGGAG 240

CCACCATTCT CCGATGAATC TTGCAGTCCA GTTTCTTGTG GGAAACCAGA AAGTCCAGAA 300

CATCGATTTG TGGTTGGCAG TAAATACACC TTTGCAAAGC ACAATTATTT ATCAGTGTGA 360

GCCTGGCTAT GAACTGGAGG GGAACAGGGC AACGTGTCTG CCAGGAGAAC AGACAGTGGA 420

```
GTGGAGGGGT GGCAATATGC AAAGAGACCA GGTGTGAAAC TCCACTTGAA TTTCTCAATG     480
GGAAAGCTGA CATTGAAAAC AGGACGACTG GACCCAACGT GGTATATTCC TGCAACAGAG     540
GCTACAGTCT TGAAGGGCCA TCTGAGGCAC ACTGCACAGA AAATGGAACC TGGAGCCACC     600
CAGTCCCTCT CTGCAAACCA AATCCATGCC CTGTTCCTTT TGGTGATTCC CGAGAATGCT     660
CTGCTGTCTT GAAAAGGAGT TTTATGTTGA TCAGAATGTG TCCATCAAAT GTAGGGAAGG     720
TTTTCTGCTG CAGGGCCACG GCATCATTAC CTGCAACCCC GACGAGACGT GGACACAGAC     780
AAGCGCCAAA TGTGAAAAAA TCTCATGTGG TCCACCAGCT CACGTAGCAA AATGCAATTG     840
CTCGAGGCGT ACATTATCAA TATGGAGACA TGATCACCTA CTCATGTTAC AGTGGATACA     900
TGTTGGAGGG TTTCCTGAGG AGTGTTTGTT TAGAAAATGG AACATGGACA TCACCTCCTA     960
TTTGCAGAGC TGTCTGTCGA TTTCCATGTC AAGAATGGGG GCATCTGCCA ACGCCCAAAT    1020
GCTTGTTCCT GTCCAGAGGG CTGGATGGGG CGCCTCTTGT GAAGAACCAA TCTGCATTCT    1080
TCCCTGTCTG AACGGAGGTC GCTGTGTGGC CCCTTACCAG TGTGACTGCC CGCCTGGCTG    1140
GACGGGGTCT CGCTGTCAAA CAAGCTGTTT GCCAGTCTCC CTGCTTAAAT GGTGGAAAAT    1200
GTGTAAGACC AAACCGATGT CACTGTCTTT CTTCTTGGAC GGGACATAAC TGTTCCAGGA    1260
AAAGGAGGAC TGGGTTTTAA CCACTGCACG ACCATCTGGC TCTCCCCAAA GCAGGATCAT    1320
CTCTCCTCGG TAGTGCCTGG GCATCCTGGA ACTTATGCGA AGAAAGTCCA ACATGGTGCT    1380
GGGTCTTGTT TAGTAAACTT GTTACTTGGG GTTACTTTTT TTATTTTGTG ATAAATTTTG    1440
TTATTCCTTG TGACAAACTT TCTTACATGT TTCCATTTTT AAATATGCCT GTATTTTCTA    1500
AATAAAAATT ATATTAAATA GATGCTGCTC TACCCTCACC AAATGTACAT ATTCTGCTGT    1560
CTATTGGGAA AGTTCCTGGT ACACATTTTT ATTCAGTTAC TTAAAATGAT TTTTTCCATT    1620
AAAGTATATT TTGCTACT                                                  1638
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 794 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 791 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
GAATTCTGCG GCCGCGAACT GCTGGCTGCC CACGGTACTC TGGAGCTGCA AGCCGAGATC    60
CTGCCCCGCC GGCCTCCCAC GCCGGAGGCC CAGAGCGAAG AGGAGAGATC CGATGAGGAG   120
CCGGAGGCCA AAGAAGAGGA AGAGGAAAAA CCACACATGC CCACGGAATT TGATTTTGAT   180
GATGAGCCAG TGACACCAAA GGACTCCCTG ATTGACCGGA GACGCACCCC AGGAAGCTCA   240
GCCCGGAGCC AGAAACGGGA GGCCCGCCTG GACAAGGTGC TGTCGGACAT GAAGAGACAC   300
AAGAAGCTGG AGGAGCAGAT CCTTCGTACC GGGAGGGACC TCTTCAGCCT GGACTCGGAG   360
GACCCCAGCC CCGCCAGCCC CCCACTCCGA TCCTCCGGGA GTAGTCTCTT CCCTCGGCAG   420
CGGAAATACT GATTCCCACT GCTCCTGCCT CTAGGGTGCA GTGTCCGTAC CTGCTGGAGC   480
CTGGGCCCTC CTTCCCCAGC CCAGACATTG AGAAACTTGG GAAGAAGAGA GAAACCTCAA   540
GCTCCCAAAC AGCACGTTGC GGGAAAGAGG AAGAGAGAGT GTGAGTGTGT GTGTGTGTTT   600
TTTCTATTGA ACACCTGTAG AGTGTGTGTG TGTGTTTTCT ATTGAACACC TATAGAGAGA   660
GTGTGTGTGT TTTCTATTGA ACATCTATAT AGAGAGAGTG TGTGAGTGTG TGTTTTCTAT   720
TGGACACCTA TTCAGAGACC TGGACTGGAT TTTCTGAGTC TGAAATAAAA GATGCAGAGC   780
TATCATCTCT T
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 795 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
GAATTCTGCG GCCGCGTGGG GACTGAGGAG GATGGCGGAG GCGTCGGCCA CAGGACGGTG    60
TACTTGTTTG ATCGGCGCGA AAAGGAGTCC GAGCTCGGGG ACCGGCCTCT GCAGGTCGGG   120
GAGCGCTCGG ACTACGCGGG ATTTCGCGCG TGTGTGTGTC AGACACTTGG CATTTCACCT   180
```

```
GAAGAAAAAT TTGTTATTAC AACAACAAGT AGGAAAGAAA TTACCTGTGA TAATTTTGAT    240
GAAACTGTTA AAGATGGAGT CACCTTATAC CTGCTACAGT CGGTCAATCA GTTACTACTG    300
ACAGCTACGA AAGAACGAAT TGACTTCTTA CCTCACTATG ACACACTGGT TAAAAGTGGC    360
ATGTATGAAT ATTATGCCAG TGAAGGACAA AATCCTTTGC CATTTGCTCT TGCGGAATTA    420
ATTGACAATT CATTGTCTGC TACTTCTCGT AACATTGGGG TTAGAAGAAT ACAGATCAAA    480
TTGCTTTTTG ATGAAACACA AGGAAAACCT GCTGTTGCAG TGATAGATAA TGGAAGAGGA    540
ATGACCTCTA AACAGCTTAA CAACTGGGCC GTGTATAGGT TGTCAAAATT CACAAGGCAA    600
GGTGACTTTG AAAGTGATCA TTCAGGATGT TCGTCCAGTA CCAGTGCCAC GCAGTTTAAA    660
TAGTGATATT TCCTATTTGG GTGTTGGGGG CAAGCAAGCT GTCTTCTTTG GTTGGGACAA    720
TCAGCCAGAA TGATAAGCCA ACCTGCAGAT TCCCCAGATG TTCACGAGCT TGTGCTTTGC    780
TAAAGGAGAT TTTGG                                                     795
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 305 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
GAATTCTGCG GCCGCGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG     60
AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG    120
AGAGAGAGAG AGAGAGAGAG AGAGAGCATT CGGCCCGATA TGTCTCGCTC CGTGGCCTTA    180
GATGTTCTCG CTCTACTCTC TCTCTCTTGC CTGGAGGCTA TCCAGGTTGC TCCCATAGAT    240
TCATGACCTC TCACCTTCTC CAAGAGATTT GGGTGCAACC AAATTGCCGG GATCCAATCT    300
TTTCC                                                                305
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 305 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
GAATTCTGCG GCCGCCTGCC CCACAACTTT CTCACGGTGG CGCCTGGACA CAGTAGTCAC    60
CACAGTCCAG GCCTGCAGGG CCAGGGTGTG ACCCTGCCCG GGGAGCCACC CCTCCCTGAG   120
AAGAAGCGGG TCTCGGAGGG GGATCGTTCT TTGGTTTCAG TCTCTCCCTC CTCCAGTGGT   180
TTCTCCAGCC CGCACAGCGG GAGCAACATC AGTATCCCCT TCCCATATGT CCTTCCCGAC   240
TTTTCCAAGG CTTCAGAAGG GGGCTCAACT CTGCAGATTG TCCAGGTGAT AAACTTGTGA   300
TCGGG                                                               305
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 424 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
GAATTCTGCG GCCGCCGCCG TCCTCCGGCT GACAGGGGGA GGAGCCCGCC GGGAGGGCCG    60
GGGTCTCGGA CTGGGGAGCC GGGACGGGAG AGCAGCGCAG CCGGGTGCAC CGCGGCCGCG   120
CCCCGGGAGG GCTGTTCGGG TCAGCGCCCA CCGCTGCTCC GCGCTGACAG CGCCGGACTG   180
GGGCGGTGCG GGGGGCTTTG CAGGCCGCCA GTGTCGACAT ACTGCTGGAG GAGGTTCGCC   240
CCGCGACCGG CTGAGTGGGG CGGCGGCCCG GGGCGACGTA CAGGAGGTTT CGCCGTCTTT   300
CTGCAACCCC CGATTTTGTT GTCATCCCCG ACGGCCCTCC AACCCTCTTT CGATAATCTA   360
CGGTGTCTTC CAAGCTCAAT TCACTGTTTT GGCAAGCAAC CCCCCATTCC CCCCTTGTAG   420
CTTG                                                                424
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3407 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
GGCGAGCACT GGCTACGTGC GACTGTGGGG AGCGGCGCGG TGCTGGGTGC TGCGGCGGCC    60
GATGCTGGCC GCCGCCGGGG GGCGGGTTCC CACTGCAGCA GGAGCGTGGT TGCTCCGAGG   120
CCAGCGGACC TGCGACGCCT CTCCTCCTTG GGCACTGTGG GGCCGAGGCC CGGCAATTGG   180
GGGCCAATGG CGGGGGTTTT GGGAAGCGAG CAGCCGCGGC GGAGGCGCAT TCTCGGGGGG   240
CGAGGACGCC TCCGAGGGCG GCGCGGAGGA AGGAGCCGGC GGCGCGGGGG GCAGCGCGGG   300
CGCCGGGGAA GGCCCGGTCA TAACGGCGCT CACGCCCATG ACGATCCCCG ATGTGTTTCC   360
GCACCTGCCG CTCATCGCCA TCACCCGCAA CCCGGTGTTC CCGCGCTTTA TCAAGATTAT   420
CGAGGTTAAA AATAAGAAGT TGGTTGAGCT GCTGAGAAGG AAAGTTCGTC TCGCCCAGCC   480
TTATGTCGGC GTCTTTCTAA AGAGAGATGA CAGCAATGAG TCGGATGTGG TCGAGAGCCT   540
GGATGAAATC TACCACACGG GGACGTTTGC CCAGATCCAT GAGATGCAGG ACCTTGGGGA   600
CAAGCTGCGC ATGATCGTCA TGGGACACAG AAGAGTCCAT ATCAGCAGAC AGCTGGAGGT   660
GGAGCCCGAG GAGCCGGAGG CGGAGAACAA GCACAAGCCC CGCAGGAAGT CAAAGCGGGG   720
CAAGAAGGAG GCGGAGGACG AGCTGAGCGC CAGGCACCCG GCGGAGCTGG CGATGGAGCC   780
CACCCCTGAG CTCCCGGCTG AGGTGCTCAT GGTGGAGGTA GAGAACGTTG TCCACGAGGA   840
CTTCCAGGTC ACGGAGGAGG TGAAAGCCCT GACTGCAGAG ATCGTGAAGA CCATCCGGGA   900
CATCATTGCC TTGAACCCTC TCTACAGGGA GTCAGTGCTG CAGATGATGC AGGCTGGCCA   960
GCGGGTGGTG GACAACCCCA TCTACCTGAG CGACATGGGC GCCGCGCTCA CCGGGGCCGA  1020
GTCCCATGAG CTGCAGGACG TCCTGGAAGA GACCAATATT CCTAAGCGGC TGTACAAGGC  1080
CCTCTCCCTG CTGAAGAAGG AATTTGAACT GAGCAAGCTG CAGCAGCGCC TGGGGCGGGA  1140
GGTGGAGGAG AAGATCAAGC AGACCCACCG TAAGTACCTG CTGCAGGAGC AGCTAAAGAT  1200
CATCAAGAAG GAGCTGGGCC TGGAGAAGGA CGACAAGGAT GCCATCGAGG AGAAGTTCCG  1260
GGAGCGCCTG AAGGAGCTCG TGGTCCCCAA GCACGTCATG GATGTTGTGG ACGAGGAGCT  1320
GAGCAAGCTG GGCCTGCTGG ACAACCACTC CTCGGAGTTC AATGTCACCC GCAACTACCT  1380
AGACTGGCTC ACGTCCATCC CTTGGGGCAA GTACAGCAAC GAGAACCTGG ACCTGGCGCG  1440
GGCACAGGCA GTGCTGGAGG AAGACCACTA CGGCATGGAG GACGTCAAGA AACGCATCCT  1500
GGAGTTCATT GCCGTTAGCC AGCTCCGCGG CTCCACCCAG GGCAAGATCC TCTGCTTCTA  1560
TGGCCCCCCT GGCGTGGGTA AGACCAGCAT TGCTCGCTCC ATCGCCCGCG CCCTGAACCG  1620
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AGAGTACTTC CGCTTCAGCG TCGGGGGCAT GACTGACGTG GCTGAGATCA AGGGCCACAG 1680

GCGGACCTAC GTGGGCGCCA TGCCCGGGAA GATCATCCAG TGTTTGAAGA AGACCAAGAC 1740

GGAGAACCCC CTGATCCTCA TCGACGAGGT GGACAAGATC GGCCGAGGCT ACCAGGGGGA 1800

CCCGTCGTCG GCACTGCTGG AGCTGCTGGA CCCAGAGCAG AATGCCAACT TCCTGGACCA 1860

CTACCTGGAC GTGCCCGTGG ACTTGTCCAA GGTGCTGTTC ATCTGCACGG CCAACGTCAC 1920

GGACACCATC CCCGAGCCGC TGCGAGACCG TATGGAGATG ATCAACGTGT CAGGCTACGT 1980

GGCCCAGGAG AAGCTGGCCA TTGCGGAGCG CTACCTGGTG CCCCAGGCTC GCGCCCTGTG 2040

TGGCTTGGAT GAGAGCAAGG CCAAGCTGTC ATCGGACGTG CTGACGCTGC TCATCAAGCA 2100

GTACTGCCGC GAGAGCGGTG TCCGCAACCT GCAGAAGCAA GTGGAGAAGG TGTTACGGAA 2160

ATCGGCCTAC AAGATTGTCA GCGGCGAGGC CGAGTCCGTG GAGGTGACGC CCGAGAACCT 2220

GCAGGACTTC GTGGGGAAGC CCGTGTTCAC CGTGGAGCGC ATGTATGACG TGACACCGCC 2280

CGGCGTGGTC ATGGGGCTGG CCTGGACCGC AATGGGAGGC TCCACGCTGT TTGTGGAGAC 2340

ATCCCTGAGA CGGCCACAGG ACAAGGATGC CAAGGGTGAC AAGGATGGCA GCCTGGAGGT 2400

GACAGGCCAG CTGGGGGAGG TGATGAAGGA GAGCGCCCGC ATAGCCTACA CCTTCGCCAG 2460

AGCCTTCCTC ATGCAGCACG CCCCCGCCAA TGACTACCTG GTGACCTCAC ACATCCACCT 2520

GCATGTGCCC GAGGGCGCCA CCCCCAAGGA CGGCCCAAGC GCAGGCTGCA CCATCGTCAC 2580

GGCCCTGCTG TCCCTGGCCA TGGGCAGGCC TGTCCGGCAG AATCTGGCCA TGACTGGCGA 2640

AGTCTCCCTC ACGGGCAAGA TCCTGCCTGT TGGTGGCATC AAGGAGAAGA CCATTGCGGC 2700

CAAGCGCGCA GGGGTGACGT GCATCATCCT GCCAGCCGAG AACAAGAAGG ACTTCTACGA 2760

CCTGGCAGCC TTCATCACCG AGGGCCTGGA GGTGCACTTC GTGGAACACT ACCGGGAGAT 2820

CTTCGACATC GCCTTCCCGG ACGAGCAGGC AGAGGCGCTG GCCGTGGAAC GGTGACGGCC 2880

ACCCCGGGAC TGCAGGCGGC GGATGTCAGG CCCTGTCTGG GCCAGAACTG AGCGCTGTGG 2940

GGAGCGCGCC CGGACCTGGC AGTGGAGCCA CCGAGCGAGC AGCTCGGTCC AGTGACCCAG 3000

ATCCCAGGGA CCTCAGTCGG CTTAATCAGA GTGTGGCATA GAAGCTATTT AATGATTAAA 3060

GTCATTTGCA GTGGGAGTTA GCATCACTAA CCTGACAGTT GTTGCCAGGA ATTTGCTTTG 3120

TTTACTGCTA GTATATTAGA AATCCTAGAT CTCAGAATCA CAATAGTAAT AAACAACAGG 3180

GGTCATTTTT TCCTAACTTA CTCTGTGTTC AGGTGTGGAA TTTCTGTCTC CCAAGAGGAA 3240

ATGTGACTTC ACTTTGGTGC CAATGGACAG AAAATTCTAC CTGTGCTACA TAGGAGAAGT 3300

TTGGAATGCA CTTAATAGCT GGTTTTTACA CCTTGATTTC GAGGTGGAAA GAAATTGATC 3360

ATGAATCTCT AATAAATTTA AATCTCTTAA ACCAAAAAAA AAAAAAA 3407

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 450 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GAATTCTGCG GCCGCACTGG AGAACCCTGC TGTGACTGGG TGGGAGATGA GGGAGCAGGC 60

CACTTCGTGA AGATGGTGCA CAACGGGATA GAGTATGGGG ACATGCAGCT GATCTGTGAG 120

GCATACCACC TGATGAAAGA CGTGCTGGGC ATGGCGCAGG ACGAGATGGC CCAGGCCTTT 180

GAGGATTGGA ATAAGACAGA GCTAGACTCA TTCCTGATTG AAATCACAGC CAATATTCTC 240

AAGTTCCAAG ATACCGATGG CAAACACCTG CTGCCAAAGA TCARGGACAG CGCGGGGCAG 300

AAGGGCACAG GGAAGTGGAC CGCCATCTTC GCCCTGGGAT TACGGGGTAC CCGTCACCCT 360

CATTGGGGAA GGTGTCTTTG STCGGTGCTT ATCATCTCTT GAAGGATGAG AGAATTTCAA 420

GCTTGCAAAA AAGTTGAGGG GTCCCCAGAA 450

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8201 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTAAAAATAC CATTAAGTAA TAGTATTAGC TTTTGTATTC TGAGATTCAA CAGCAGCAGT 60

CACTTCCCTC CACTCCTATG TGTATCCCAG GACCACCCTG GGCGGGGAGG GCTGAGGTCA 120

GGGAGGTCTG AAGCTGGTCC TGGGCTCCGG GGGTGACAGT GATGAGGAAC TGGGTGCACA 180

CATGAGTGGG GCAGCCGGGC CTGGCCAGAG AAGCAACACA CACGTGCACA GACATGTTTA 240

TCCACATACA CATGTGCACG CATGTGCACA AACACATTGC AGGCAGGCAT GTTGACGCCT 300

CAGGCAGCGG AGGACCCTGA CTCTGGGCCC TGCTGACCCG GGCAAGGCCC ATTGTGATGC 360

GTGCCATGAC CTCAGAATGT CACTGGTGCT TAGCACCTAT CCGCTCTCCA GACTGCGTCT 420

GTGTTCTACG GCAGTTACAC ACACGCAGTG GTATTCACAA GCGGTTTTGT GGACTCAAAG 480

GTTTTCTCCC TGAGAGGCAT AACCCAGGCC AGCTGATTCA TCAGAATCAG GTGAGTGTGA 540

CCTGCTCTCT TCCCTCCAGG CTGACTTGGG GACAGTGGCT ATGGTATGGG CGGTGTTGGC 600

CTCTGGGCAG CTACAGAGGA GGGTCATCCC TGAGCACTCA CCGGGCGCCC GTTCTACACT 660

GCCCATGTAG ACGATTTTCT CTTTCGTCTT CATGGTGGCT TCGTAGAGTG GGTGCTGTTC 720

CCAAATGTAC CCATTCGACA GGTGAGCCGT CTGGGGTCAG AGAGGCAGTA ACTGGCCTGG 780

GAATCCAGAC AAGACCCTGG GTTTTGCTCT CAGCCCTGCT GTGTGCCATG CTAGACTTCA 840

GGCCTCAACC CTGAGACCTC CCTGCTCTAG ATCCCAAATC TGCCCAGATT TCCGATCCAA 900

TGGGCAGAGC CTGGCCCTGG CAGAGACACT GGGATGGATC CACTGTGGGT GGGGAGGAGG 960

GAAGGGTCCT CAGAACACAC CTGGGGCCTA AGCTGGGTCT TGATGGTCAC TGTGGGACCC 1020

ACTGGACACA CACAGTCCCT TGTCTGGGAG TGGCATGGGG AGCCTTCTGC CCTTGGGCAG 1080

TTGTGGAAAG TGAAGGAGCC CTGGAGAGCT GGCTGAGGGG AGACTATCTT CCCTTGTGTT 1140

CAAAGGGGTC CAGGCACTGG GGCTCTCCCC AAGTATTTCT TATTCTGTCT GGCCTCGCTT 1200

TCCTTTTGCC CTGAGTATTC TCAGGAGGGA CGGTCCATCT AGATGTCCTC CAGGAGCAAG 1260

GACCCACTGT TCTTCATCAG TGACCCAGGA AAATGAAGCC CCCTCCTGTG GGGACAGCTC 1320

AGAATGGTGG AGTCCACAGT CCCTCCCTGA GAGACATGGT TTCCATGAGC ACAGTGGCTG 1380

CTTTGGAGAC AGTAATCATT TTCATCCCCA AAACCAAACA CACTCCTGCT CAAATGGTGT 1440

TATTGCTAAA GCAGCTTCAC TGGTTAGACT GAAGGGCCAT GGTAGCCCAA GTGATGAGCG 1500

GGGTAGAATG GAGCAGTCAG GAGAGATCTT GTTCCCCGTA GGAAACTGGG CATCTCTGTG 1560

GCCCTGAACA TCCCAGGAGG CCGATCGTAC AGAGACCTCT GGTGCCTGAC CGCAGTTCAC 1620

ATCCACATCC CTGGAATAGA CCATCACAGG CTCTTCACCC TTGGCAGGTG GACACCATTC 1680

AACCTGCCGG GGCAGGATGG ACATGGTAGA GAATGCAGAT AGTTTGCAGG CACAGGAGCG 1740

GAAGGACATA CTTATGAAGT ATGACAAGGG ACACCGAGCT GGGCTGCCAG AGGACAAGGG 1800

GCCTGAGCCC GTTGGAATCA ACAGCAGCAT TGATCGTTTT GGCATTTTGC ATGAGACGGA 1860

GCTGCCTCCT GTGACTGCAC GGGAGGCGAA GAAAATTCGG CGGGAGATGA CACGAACGAG 1920

CAAGTGGATG GAAATGCTGG GAGAATGGGA GACATATAAG CACAGTAGCA AACTCATAGA 1980

TCGAGTGTAC AAGGGAATTC CCATGAACAT CCGGGGCCCG GTGTGGTCAG TCCTCCTGAA 2040

CATTCAGGAA ATCAAGTTGA AAAACCCCGG AAGATACCAG ATCATGAAGG AGAGGGGCAA 2100

GAGGTCATCT GAACACATCC ACCACATCGA CCTGGACGTG AGGACGACTC TCCGGAACCA 2160
TGTCTTCTTT AGGGATCGAT ATGGAGCCAA GCAGAGGGAA CTATTCTACA TCCTCCTGGC 2220
CTATTCGGAG TATAACCCGG AGGTGGGCTA CTGCAGGGAC CTGAGCCACA TCACCGCCTT 2280
GTTCCTCCTT TATCTGCCTG AGGAGGACGC ATTCTGGGCA CTGGTGCAGC TGCTGGCCAG 2340
TGAGAGGCAC TCCCTGCCAG GATTCCACAG CCCAAATGGT GGGACAGTCC AGGGGCTCCA 2400
AGACCAACAG GAGCATGTGG TACCCAAGTC ACAACCCAAG ACCATGTGGC ATCAGGACAA 2460
GGAAGGTCTA TGCGGGCAGT GTGCCTCGTT AGGCTGCCTT CTCCGGAACC TGATTGACGG 2520
GATCTCTCTC GGGCTCACCC TGCGCCTGTG GGACGTGTAT TTGGTGGAAG GAGAACAGGT 2580
GTTGATGCCA ATAACCAGCA TTGCTCTTAA GGTTCAGCAG AAGCGCCTCA TGAAGACATC 2640
CAGGTGTGGC CTGTGGGCAC GTCTGCGGAA CCAATTCTTC GATACCTGGG CCATGAACGA 2700
TGACACCGTG CTCAAGCATC TTAGGGCCTC TACGAAGAAA CTAACAAGGA AGCAAGGGGA 2760
CCTGCCACCC CCAGGCCCAA CAGCCCTGGG ACGAAGGTGT GTGGCAGGAA GCCCCCAGCC 2820
AGTCTGAACC CTGGGGGCAG TCCCAGGAGC CACCCACCAT GCCCCAACGG CTTCCCCATG 2880
CCAGGCAGCA CACACCCCTC CCTCTGGGAT CAGCAGACTA CAGGCGTGTC GTCAGTGTCA 2940
GACCACAGGG GCCACACAGA GACCCCAAGG ACTCCAGAGA TGCAGCCAAA CGCGAGCAAG 3000
GGTCCTTGGC ACCCAGGCCT GTGCCGGCTT CACGTGGTGG GAAGACCCTC TGCAAGGGGT 3060
ATAGGCAGGC CCCTCCAGGC CCACCAGCCC AGTTCCAGCG GCCCATTTGC TCAGCTTCCC 3120
CGCCATGGGC ATCTCGTTTT TCCACGCCCT GTCCTGGTGG GGCTGTCCGG GAAGACACGT 3180
ACCCTGTGGG CACTCAGGGT GTGCCCAGCC TGGCCCTGGC TCAGGGAGGA CCTCAGGGTT 3240
CCTGGAGATT CCTGGAGTGG AAGTCAATGC CCCGGCTCCC AACGGACCTG GATATAGGGG 3300
GCCCTTGGTT CCCCCATTAT GATTTTGAAC GGAGCTGCTG GGTCCGTGCC ATATCCCAGG 3360
AGGACCAGCT GGCCACCTGC TGGCAGGCTG AACACTGCGG AGAGGTTCAC AACAAAGATA 3420
TGAGTTGGCC TGAGGAGATG TCTTTTACAG CAAATAGTAG TAAAATAGAT AGACAAAAGG 3480
TTCCCACAGA AAAGGGAGCC ACAGGTCTAA GCAACCTGGG AAACACATGC TTCATGAACT 3540
CAAGCATCCA GTGCGTTAGT AACACACAGC CACTGACACA GTATTTTATC TCAGGGAGAC 3600
ATCTTTATGA ACTCAACAGG ACAAATCCCA TTGGTATGAA GGGGCATATG GCTAAATGCT 3660
ATGGTGATTT AGTGCAGGAA CTCTGGAGTG GAACTCAGAA GAGTGTTGCC CCATTAAAGC 3720
TTCGGCGGAC CATAGCAAAA TATGCTCCCA AGTTTGATGG GTTTCAGCAA CAAGACTCCC 3780
AAGAACTTCT GGCTTTTCTC TTGGATGGTC TTCATGAAGA TCTCAACCGA GTCCATGAAA 3840

AGCCATATGT GGAACTGAAG GACAGTGATG GCCGACCAGA CTGGGAAGTA GCTGCAGAGG 3900

CCTGGGACAA CCATCTAAGA AGAAATAGAT CAATTATTGT GGATTTGTTC CATGGGCAGC 3960

TAAGATCTCA AGTCAAATGC AAGACATGTG GGCATATAAG TGTCCGATTT GACCCTTTCA 4020

ATTTTTTGTC TTTGCCACTA CCAATGGACA GTTACATGGA CTTAGAAATA ACAGTGATTA 4080

AGTTAGATGG TACTACCCCT GTACGGTATG GACTAAGACT GAATATGGAT GAAAAGTACA 4140

CAGGTTTAAA AAAACAGCTG AGGGATCTCT GTGGACTTAA TTCAGAACAA ATCCTACTAG 4200

CAGAAGTACA TGATTCCAAC ATAAAGAACT TTCCTCAGGA TAACCAAAAA GTACAACTCT 4260

CAGTGAGCGG ATTTTTGTGT GCATTTGAAA TTCCTGTCCC TTCATCTCCA ATTTCAGCTT 4320

CTAGTCCAAC ACAAATAGAT TTCTCCTCTT CACCATCTAC AAATGGAATG TTCACCCTAA 4380

CTACCAATGG GGACCTACCC AAACCAATAT TCATCCCCAA TGGAATGCCA AACACTGTTG 4440

TGCCATGTGG AACTGAGAAG AACTTCACAA ATGGAATGGT TAATGGTCAC ATGCCATCTC 4500

TTCCTGACAG CCCCTTTACA GGTTACATCA TTGCAGTCCA CCGAAAAATG ATGAGGACAG 4560

AACTGTATTT CCTGTCACCT CAGGAGAATC GCCCCAGCCT CTTTGGAATG CCATTGATTG 4620

TTCCATGCAC TGTGCATACC CAGAAGAAAG ACCTATATGA TGCGGTTTGG ATTCAAGTAT 4680

CCTGGTTAGC AAGACCACTC CCACCTCAGG AAGCTAGTAT TCATGCCCAG GATCGTGATA 4740

ACTGTATGGG CTATCAATAT CCATTCACTC TACGAGTTGT GCAGAAAGAT GGGATCTCCT 4800

GTGCTTGGTG CCCACAGTAT AGATTTTGCA GAGGCTGTAA AATTGATTGT GGGGAAGACA 4860

GAGCTTTCAT TGGAAATGCC TATATTGCTG TGGATTGGCA CCCCACAGCC CTTCACCTTC 4920

GCTATCAAAC ATCCCAGGAA AGGGTTGTAG ATAAGCATGA GAGTGTGGAG CAGAGTCGGC 4980

GAGCGCAAGC CGAGCCCATC AACCTGGACA GCTGTCTCCG TGCTTTCACC AGTGAGGAAG 5040

AGCTAGGGGA AAGTGAGATG TACTACTGTT CCAAGTGTAA GACCCACTGC TTAGCAACAA 5100

AGAAGCTGGA TCTCTGGAGG CTTCCACCCT TCCTGATTAT TCACCTTAAG CGATTTCAAT 5160

TTGTAAATGA TCAGTGGATA AAATCACAGA AAATTGTCAG ATTTCTTCGG GAAAGTTTTG 5220

ATCCGAGTGC TTTTTTGGTA CCACGAGACC CGGCCCTCTG CCAGCATAAA CCACTCACAC 5280

CCCAGGGGGA TGAGCTCTCC AAGCCCAGGA TTCTGGCAAG AGAGGTGAAG AAAGTGGATG 5340

CGCAGAGTTC GGCTGGAAAA GAGGACATGC TCCTAAGCAA AAGCCCATCT TCACTCAGCG 5400

CTAACATCAG CAGCAGCCCA AAAGGTTCTC CTTCTTCATC AAGAAAAAGT GGAACCAGCT 5460

GTCCCTCCAG CAAAAACAGC AGCCCTAATA GCAGCCCACG GACTTTGGGG AGGAGCAAAG 5520

GGAGGCTCCG GCTGCCCCAG ATTGGCAGCA AAAATAAGCC GTCAAGTAGT AAGAAGAACT 5580

TGGATGCCAG CAAAGAGAAT GGGGCTGGGC AGATCTGTGA GCTGGCTGAC GCCTTGAGCC 5640
GAGGGCATAT GCGGGGGGGC AGCCAACCAG AGCTGGTCAC TCCTCAGGAC CATGAGGTAG 5700
CTTTGGCCAA TGGATTCCTT TATGAGCATG AAGCATGTGG CAATGGCTGT GGCGATGGCT 5760
ACAGCAATGG TCAGCTTGGA AACCACAGTG AAGAAGACAG CACTGATGAC CAAAGAGAAG 5820
ACACTCATAT TAAGCCTATT TATAATCTAT ATGCAATTTC ATGCCATTCA GGAATTCTGA 5880
GTGGGGGCCA TTACATCACT TATGCCAAAA ACCCAAACTG CAAGTGGTAC TGTTATAATG 5940
ACAGCAGCTG TGAGGAACTT CACCCTGATG AAATTGACAC CGACTCTGCC TACATTCTTT 6000
TCTATGAGCA GCAGGGGATA GACTACGCAC AATTTCTGCC AAAGATTGAT GGCAAAAAGA 6060
TGGCAGACAC AAGCAGTACG GATGAAGACT CTGAGTCTGA TTACGAAAAG TACTCTATGT 6120
TACAGTAAAG CTACCACTCT GGCTGCTAGA CAGCTTGGTG GCGAGGGAGA TGACTCCTTG 6180
TAGCTGATAC TTGGCAAAAG TGTCACTGAA AGACAAGCTA AATGTAGTTA TTTTATCCTG 6240
TTAGAACAAA AATTCTAATT AAAATAGTTA ACTTGAAGAG TAGAAACAAT TGTATTTTGA 6300
AGTCTCATAC AAGCTGTCTG ATAGAGAACT TTCAGGCAGA TCCCACCATT AGCCTGTAAA 6360
CAAAAGGTGT GGCACCAGCC ACCTGGGACC AAATAAGAAT TGAATTGTGC TTGTCCAGAT 6420
ATGAACAAAT ATGTAGTGAG TATAGAGTTT ACCAATAATC ATAACAAATA TTAAAGATTT 6480
CCTTGGAGTC AGAGGAAAAA ACAAACAATT ATAATGTTGT CTAGGGACGA CATGATACGC 6540
TACCTCCTTT TTCCTGAAGT TTTATTCCAT TATATTGACA AGATGGAGAA AGCAAGATCA 6600
TGAAGGTGTG CAAATGATTC TTACGGCATG GACAAGGATT TTTCAATTTA TTTTTTAAAC 6660
TGTTTCCATA CCCTTTCTTT TTCTTGCTTT TTGTTTTTGC CATTGTGTTT ACGTTTGAGA 6720
CACAACCAGT CATTGGTGGC AGGGGCATAG AGTGGTCAGT CTGAAAGGGA GGCTCTCTTA 6780
AGAGCTATGT GCCTTCCAAC CAGAGGGAGA CCCAGTAGAA AGAAAAACAT CCTGGGAAAT 6840
CCAGCTACCA GGGCCCTCCC AGTGGAGGCA TCTTACATTT AGGCTACTTC AAGTATCCTC 6900
AGAAATGTAT TCTGCACCCC CGGCCCCGCC CATGCTGAGG GAAGGGGAGC AGTTGCCAAT 6960
ATTTGCACCA TCTTCACATG CACATGTTGC AACAAGAGCT TCTGGGAAGG TAAGCGGCAT 7020
CGGAGCTAGA TCACGTTTCA CAATTAGTGG TTATTCTTTT CTGTGTTTGT TTTGCACTTT 7080
AAAAAAGAGA GAACACATGC AAATGAACTT GCTTGTGTGT ATTTGATGGC TCTAAGGGCT 7140
ATAAATTACA AACAAAACAC ATCCCAGACA TTAGGAGTTC ATAAGTATAT TTAATGAAAT 7200
TGGTGGTTTT AGGAAGTCAA CTTTAGTTTT GCTTTGTTTG CATGTCCACT GGTTTTTTTA 7260
TTTTGATATT TGTCTTTTTT TAAATTTTAC AGTAGTCATT GAAAGTTATG TTTCTTTGCT 7320

TACTTCATTT TTTCCCTCTA ATTATTTAAG ATTGGAACAA AAGTATAAAT ATTATTTATT 7380

TGAGGTAGAA TTTTTTTCAT GTAGTTTCTT AATATATACT TGAAGGAAAT GTTTCACCTT 7440

ATTTTTGGTC TTTGTTTATT CATTTAGACC CTGCAAGTTG ATTCTCATTG CCAGATTCCA 7500

TTACCCTTTC TTCCTCATAG GTAGTAATTA CCAATGTAAC TAAGCATTTG TGTTCTGATA 7560

TCTGAGGCCA GTAACTATTA ATATCTAGTT CTCAGAGCAT TTGGAAAGGT TATCTTAAAT 7620

GGCTACCTAA ATTGAAATCC TTTTCAGAAA AAATATAATT GCAAGTAGGT AGGAGTGGCC 7680

TAAATTGTCT AATGTAATAA AGTCAGACAA AATGCACACT TTATAGTTTC AAGATTTTCA 7740

GTAAATAAAA TCTGTCCATT CCTACCTGGA CATGTCCCAT TAAAAAGTGG AAGATTTTAA 7800

ATAATTTCTT TACAGATGTT TTATTTAAAC AGGTAGCACA ATCTACTAAT GTTGTGTGAT 7860

TTGTGTTATA CTGGTTGTAA TTAATTTTTT TAATTCATGA ACTAGCGGAA AATTTATTAA 7920

ATTAACTATT AACTACATTC ACCTTGTAAA TTACTGTATA AAACTTGTTG ACAATGCACT 7980

GACTTTAGAA AGATGTTAAT GTACATAAAT AGAGTGTAAA TAAAATAGTG TTGATGTACT 8040

GAAATATGAA CTGTATCAAA AGTATTGGTA ATTGTATATG GGGTGTACCT GTTTATCTGT 8100

TAACTATTAT CCAAACAAAT TAAATACTGT GGTTGCCTCT ATGTGCTGTT TTTCCTCATA 8160

CAAGTAAACA CAGAAAGTCA AAAAAAAAAA AAAAAAAAAA A 8201

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 945 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GAATTCTGCG GCCGCCAGAA AATTCACAAA GAGATGCCCT GTAAGTGTAC TGTATGTGGC 60

AGTGACTTCT GCCATACTTC ATACCTACTT GAACATCAGA GGGTCCATCA TGAAGAGAAA 120

GCCTATGAGT ATGATGAATA TGGGTTGGCC TATATTAAAC AACAAGGAAT TCATTTCAGA 180

GAAAAGCCCT ATACGTGTAG TGAATGTGGA AAAGACTTCA GATTGAATTC ACATCTTATT 240

CAGCATCAAA GAATTCACAC AGGAGAGAAA GCACATGAAT GTCATGAATG TGGAAAAGCT 300

TTCAGTCAAA CCTCATGCCT TATTCAGCAT CACAAAATGC ATAGGAAAGA GACTCGTATT 360

GAATGTAATG AGTATTGAGG GCAGGTTCAA GTCATAGCTC AGATCTTATC CTGCAACAAG 420

GAAGTCCTCA CCAGACAGAA AGCCTTTGAT TGGTGATGTA TGGGAAAAGA ACTCCAGTCA 480

GAGAGCACAT CTAGTTCAAC ATCAGAGCAT TCATACCAAA GAGAACTCAT GAATGTAATG 540

AAGATGGGAA GATATTTATC AAATTCAGGC TTCATTCAGC ATCTGAGAGT TCACACCAGG 600

GAGCAAATCA TGTATGTACT GCATGTGGTA AAGCCTTCAG TCATAGCTCA GCCATTGCTC 660

AGCATCAGAT AATTCACACC AGAGAGAAAC CCTCTGAATG TGACGAATGA AGAAAAGGTA 720

TTAGTGTTAA ACTCTTAATC GACTCCTGCA AATCTATACC AGTGAGAAAT CTTACAAATG 780

TATTGGATTG TGGCAAATTT CTCATGCTAT TAGTATTTTC ATACCTTAGT CACATGTGGG 840

GGAATCCACA TGGGAATAAA CTCCCATTGC TGCAATGATT GTGAAAAGCA TCAGGCAAGG 900

AACTTCCTGG TTAGGTTCAA TTCCACGCCA TGCAAAAGGT TTTTA 945

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 971 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GAATTCTGCG GCCGCCTCTT CGCTGAGGCG GGGCCAGACT TTGAACTGCG GTTAGAGCTG 60

TATGGGGCCT GTGTGGAAGA AGAGGGGGCC CTGACTGGCG GCCCCAAGAG GCTTGCCACC 120

AAACTCAGCA GCTCCCTGGG CCGCTCCTCA GGGAGGCGTG TCCGGGCATC GCTGGACAGT 180

GCTGGGGGTT CAGGGAGCAG TCCCATCTTG CTCCCCACCC CAGTTGTTGG TGGTCCTCGT 240

TACCACCTCT TGGCTCACAC CACACTCACC CTGGGAGGAG TGCAAGATGG ATTCCGCACA 300

CATGACCTCA CCCTTGGCAG TCATGAGGAG AACCTGCCTG GCTGCCCCTT TATGGTAGCG 360

TGTGTTGCCG TCTGGCAGCT CAGCCTCTCT GCATGACTCA GCCCACTGCA AGTGGTACCC 420

TCAGGGTGCA GCAAGCTGGG GAGATGCAGA ACTGGGCACA AGTGCATGGA GTTCTGAAAG 480

GCACAAACCT CTTCTGTTAC CGGCAACCTG AGGATGCAGA CACTGGGGAA GAGCCGCTGC 540

TTACTATTGC TGTCAACAAG GAGACTCGAG TCCGGGCAGG GGAGCTGGAC CAGGCTCTAG 600

GACGGCCCTT CACCCTAAGC ATCAGTAACC AGTATGGGGA TGATGAGGTG ACACACACCC 660

TTCAGACAGA AAGTCGGGAA GCACTGCAGA GCTGGATGGA GGCTCTTGTG GCAGCTTTTT 720

CTTTTGGACA ATGAGCCAAT GGAAGCAGTG CTTGTGATGA AATCAATGAA AATTGGAAAC 780

TTCCTGCTCC CCCGGAAACC ACCCCAAGCA CTGGCAAAGC AGGGGGTCCT TGTACCATGA 840

GATGGCTATT GAGCCGCTGG ATGACATCGC AGCGGGTGAA AGACATCCTG ACCCAGGGGG 900

AGGGCGCAAG GTTGGAGACA CCCCCCCCGG TTGGAATTTT TACAGACAGC CTGCCTGCTT 960

ACCCCTGTCG C 971

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1285 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GAATTCGGCA CGAGAGCAAG CAAGAGAAAG AGAAGAGCAA GAAGAAAAAA GGAGGTAAAA 60

CAGAACAGGA TGGCTATCAG AAACCCACCA ACAAACACTT CACGCAGAGT CCCAAGGAAG 120

TCAGTGGCCG ACCTGCTGGG GTCCTTTGGA AGGCAAACGA AGGACTCCTT CTGATCACTG 180

CTCCCAAGGC TGAGGAACAA CAACGTGATG AATATCTGGA AAGTTTCTGC AAGATGGCTA 240

CCAGGAAAAT CTCTGTGATC ACCATCTTCG GCCCTGTCAA CAACAGCACC ATGAAAATCG 300

ACCACTTTCA GCTAGATAAT GAGAAGCCCA TGCGAGTGGT GGATGATGAA GACTTGGTAG 360

ACCAGCGTCT CATCAGCGAG CTGAGGAAAG AGTACGGAAT GACCTACAAT GACTTCTTCA 420

TGGTGCTAAC AGATGTGGAT CTGAGAGTCA AGCAATACTA TGAGGTACCA ATAACAATGA 480

AGTCTGTGTT GGATCTGATC GATACTTTCC AGTCCCGAAT CAAAGATATG GAGAAGCAGA 540

AGAAGGAGGG CATTGTTTGC AAAGAGGACA AAAAGCAGTC CCTGGAGAAC TTCCTATCCA 600

GGTTCCGGTG GAGGAGGAGG TTGCTGGTGA TCTCTGCTCC TAACGATGAA GACTGGGCCT 660

ATTCACAGCA GCTCTCTGCC CTCAGTGGTC AGGCGTGCAA TTTTGGTCTG CGCCACATAA 720

CCATTCTGAA GCTTTTAGGC GTTGGAGAGG AAGTTGGGGG AGTGTTAGAA CTGTTCCCAA 780

TTAATGGGAG CTCTGTTGTT GAGCGAGAAG ACGTACCAGC CCATTTGGGT GAAAGACATC 840

CGTAACTATT TCAAGTGAGC CCGGAGTACT TCTCCATGCT TCTAGTCGGA AAAGACGGAA 900

ATGTCAAATC CTGGTATCCT TCCCCAATGT GGTCCATGGT GATTGTGTAC GATTTAATTG 960

ATTCGATGCA ACTTCGGAGA CAGGAAATGG CGATTCAGCA GTCACTGGGG ATGCGCTGCC 1020

CAGAAGATGA GTATGCAGGC TATGGTTACC ATAGTTACCA CCAAGGATAC CAGGATGGTT 1080

ACCAGGATGA CTACCGTCAT CATGAGAGTT ATCACCATGG ATACCCTTAC TGAGCAGAAA 1140

TATGTAACCT TAGACTCAGC CAGTTTCCTC TGCAGCTGCT AAAACTACAT GTGGCCAGCT 1200

CCATTCTTCC ACACTGCGTA CTACATTTCC TGCCTTTTTC TTTCAGTGTT TTTCTAAGAC 1260

TAAATAAATA GCCAACTTTC ACCTT 1285

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1439 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAATTCTGCG GCCGCCATTA CTCCTGCAAC ATATCTGGCT CTCTGAAGCG GCACTACAAC 60

AGGAAGCACC CTAATGAGGA GTATGCCAAC GTGGGCACCG GGGAGCTGGC AGCGGAGGTG 120

CTCATCCAGC AAGGTGGTTT GAAGTGTCCT GTTTGCAGCT TTGTATATGG CACCAAATGG 180

GAGTTCAATA GGCACTTGAA GAACAAACAT GGCTTGAAGG TGGTGGAAAT TGATGGAGAC 240

CCCAAGTGGG AGACAGCAAC AGAAGCTCCT GAGGAGCCCT CCACCCAGTA TCTCCACATC 300

ACAGAGTCCG AAGAAGACGT TCAAGGGACA CAGGCAGCGG TGGCCGCGCT CCAGGACCTG 360

AGATACACCT CTGAGAGTGG CGACCGACTG GACCCCACGG CTGTGAACAT CCTGCAGCAG 420

ATCATTGAGC TGGGCGCCGA GACCCATGAC GCCACTGCCC TTGCCTCGGT GGTTGCCATG 480

GCACCAGGGA CGGTGACTGT GGTTAAGCAG GTCACCGAGG AGGAGCCCAG CTCCAACCAC 540

ACGGTCATGA TCCAGGAGAC GGTCCAGCAA GCGTCCGTGG AGCTTGCCGA GCAGCACCAC 600

CTGGTGGTGT CCTCCGACGA CGTGGAGGGC ATTGAGACGG TGACTGTCTA CACGCAGGGC 660

GGGGAGGCCT CGGAGTTCAT CGTCTACGTG CAGGAGGCCA TGCAGCCTGT GGAGGAGCAG 720

GCCTGTGGAG CAGCCGGCCC AGGAACTCTA GAGGACATGT GGCATCGGAT GGCCACAGGG 780

CGGGGCTGTC CAGGCTCTTC AGGCACCCAG GGTGGGGAGG CCACCTTCCT GCCCTACCCG 840

AGAATGGTGT CTCCTTTGCC CTCCCTGCCC AGCAGCCTGA TAGGACTCTC CTAGTCCAAC 900

TTGGGGTGGG CAAGGCAGTC AGCATCACCA GCAACACCAC AGGACCCTCA CCCCAGCATA 960

GACACACACC CCCTGACCCT TACCATCTGC TTCCTGAAAG ACTTCAGTGT CAGCTCCCCT 1020

ACACACACCC CACACCTTCA CCCCTTGCTT CAAGATTCAA ACAGAGACTC CCAGTCCCCC 1080

TCAGCATCTT CCCTGGATCA CAACCCCAGC TCCTTGACCC CCATCTAGGT GCCAAATGTT 1140

CATCTGCAAC CGCTATGCAG TCTGGTGAGA GGGAGACAGC CATCACATAG AAAGTGGCCG 1200

TACGGGTTTT TAATCACTGC TGGGTGGGGT GGGGGTAGGG GGATTGTCCT GGCTTTGTCG 1260

ACAAAGTCCC ACTTCCCCGA GTATTAAGGG CCCTTGGTAT CAAGTGAGGT AAATTCACCC 1320

ATCACAGGGT CTCGCCCTAC CATCCTGGAA TTATTTCACT TTTAAGATAA ATGCACTATT 1380

TCACTGTTCG CCTCCCATTC TAAGGAGGTG AGGTGGTTGG AATAAAAACA GTTCCTGTC 1439

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 349 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GAATTCTGCG GNCGCGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG 60

AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG 120

AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGCCCA 180

GGTCTTAACA CATATGGGAC TGATGTCATC TCGACCTCTC CATTTATTGA GTCTGTGATT 240

TATTTGGAGT GGAGGCATCG TTTTTAAGAA ACACATGTCA TCTAGGTTGT CTAAACCTAT 300

CTGCATCTAC TCTCACCTCA NCCCCCCCCC CCCCTTCCCC CCCTNTTCC 349

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 572 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCTGCG GCCGCCGATC CGAGGTCCTT TTAGTCTCAG AGGATGGGAA GATCCTGGCA 60

GAAGCAGATG GACTGAGCAC AAACCACTGG CTGATCGGGA CAGACAAGTG TGTGGAGAGG 120

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ATCAATGAGA TGGTGAACAG GGCCAAACGG AAAGCAGGGG TGGATCCTCT GGTACCGCTG   180
CGAAGCTTGG GCCTATCTCT GAGCGGTGGG GACCAGGAGG ACGCGGGGAG GATCCTGATC   240
GAGGAGCTGA GGGACCGATT TCCCTACCTG AGTGAAAGCT ACTTAATCAC ACCGACGGCG   300
GCGGCTCCAT CGACACAGCT ACACCGGATG GTGGAGTTGT GCTCATATCT GGAACAGGCT   360
CCAACTGCAG GCTCATCAAC CCTGATGGCT CCGAGAGTGG CTGCGGGCGG CTTGGGGGCA   420
TATTATGGGT GATGAGGGTT CAGCCTACTG GATCGCACAC CAAGCAGTGA AAATAGTGTT   480
TGGACTCCAT TGAAAACTAG AGGCGGTCCC ATGATATCGG TTACGTCAAA CAGGCCATGT   540
TCCACTATTT CCAGGTTCAG ATCCGCTAGG TT                                 572
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(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 402 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

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GAATTCTGCG GCCGCCAGAG CAGCACGGAG ATCAGCAAGA CGCGGGGCGG GGAGACAAAG    60
CGCGAGGTGC GGGTGGAGGA GTCCACCCAG GTCGGCGGGG CACCCCTTCC CTGCTGTGTT   120
TGGGGACTTC CTGGGCCGGG AGCGCCTGGC ATCCTTCGGC AGTATCACCC GGCAGCAGGA   180
GGGTGAGGCC AGCTCTCAGG ACATGACTGC ACAGGTGACC AGCCCATCGG GCAAGGTGGA   240
AGCCGCAGAG ATCGTCGAGG GCGAGGACAG CGTCTACAGC GTGCGCTTTG TGCCCCAGGA   300
AATGGGGGCC CATACGGTCG GTGTCAAGTA CCGTGGNCAG CACGTGCCCG GNAGNCCCTT   360
TCAGTTCACT GTNGGGCCGC TGGGTGANGG TTGGTGCCCA CA                      402
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 771 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

AAGGGGAAGA GAAGAGAGTG TCCAGGGAGC CAGCAGGTGT CCTCTCCCAG AGTGGTATGC 60

AGCTGGAATA TCTGTCCCTC CCCTTCCAAC TTCCCGCACG CAGATCCTTG CAGGTTGAGC 120

TCTGTGGAGG CCAACCTGTC CTCTCCAGGG TGAAAGTGCA GTGGAGGCCT TCTGGCTCCA 180

CTCCAAATGT GATAGAAGGG GATCTCCTGG TATTTGGCCA GCAGCTTGCT CCTCCAATGG 240

GCATGGGGGA GGTCATGGAG GAAGAGCGCA GGTTGTGTTA ACTGTCCTTG AACATTAGCG 300

GTTTCGGCTC CTCCACCAAG TATCCGCCCA GAGTCCGCTC CAGCTCCAGC ACCTCCTTCA 360

GTGCTACAGG CCTGTCCTCC AGACAGTAGA CCCGGAGTCT GTACTCCAGG GAGGTGCAGA 420

GGGCGGGGGC GAAGACGGCC AGCTGGASCC GCTTGACTGC TGAGCGGGAA TAGGACTCGC 480

CCGTGAACAC GTAGGTGCCC AGCTGGTCCA GCAGGATGTG ACAGGCCCTG GGCTCCAGCT 540

GGCAGTAGCA GGGTGTGTTC AGGGTCTCCT CATCCAGGGT CACCACCTCC TCCCAGTGGC 600

CCTGGTGGGC CTGGGTCTTG AGCTGAAAGA TCCAGTCACG GGCACTGACT TCGGCACAGT 660

GGGGCATGGT GAGGATGACG GGGCGGCACA GCAGGAGGCC TGTGGGTCCA CAGGTCACCG 720

AGGGGCTCAA TACTGTCTCG GGAGAGGCAT AATCTGGCAC ATCATAAGGG T 771

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 638 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GAATTCTGCG GNCGCGCCCT ACATGTGAAC AACGATCGGG CAAAAGTGAT CCTGAAGCCA 60

GACAAGACTA CTATTACAGA ACCACACCAC ATCTGGCCCA CTCTGACTGA CGAAGAATGG 120

ATCAAGGTCG AGGTGCAGCT CAAGGATCTG ATCTTGGCTG ACTACGGCAA GAAAAACAAT 180

GTGAACGTGG CATCACTGAC ACAATCAGAA ATTCGAGACA TCATCCTGGG TATTGAGGAT 240

CTTCGGGAAC CGTCACAGGA GGGGGAGNAG ATCGCTGAGA TCCGAGAAGC AGGCCCAGGG 300

AACAATCGCA GGTTGACGGC AACACAGGAT TCGCACTTGT CAACAAGCAT TGGGGATGAG 360

TTCAACAACC TCCACCACCC CAGGAATTTT TGAGACCCCG GNTTTTCCTC CATCCNAGNN 420

TTTANTTGGG GGGGTCAAAG GGCCNNTTNT TTTTGCCCAC CCTGAACCCT AGGGCCCAAC 480

CCNNTTTTTT TTTCNACNTT TNGGAATNAA AGGGGNTTTG NTCANACCCC ANCCCCCCCN 540

GNTTTNNTTT NGNNGGTCCC CTTTNTTTTT TTCCCCCCNG NCCCNNTTTG NNGGTTCCTT 600

TTTGGGGGGC CCCCCNTTCN CCCCGGGNNG GGGCCCCC 638

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2056 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: -
(B) LOCATION: 176
(D) OTHER INFORMATION: /label= ATG
/note= "start codon"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGGTTTTT TTTTTTTTTT TTTTTTTTTT TTATATGCAT GGAGTTATAC 60

AGGATGTGAC TTTTTGAGAT TGGCTTTTTC CGTTGACTAT CCTGCCCCTG AGATCCACCC 120

AAGTTGTGGG ATCTGAAACT TGCCCACCCT TCGGGATATT GCAGGACGCT GCATCATGAG 180

CGACAGTAAA TGTGACAGTC AGTTTTATAG TGTGCAAGTG GCAGACTCAA CCTTCACTGT 240

CCTAAAACGT TACCAGCAGC TGAAACCAAT TGGCTCTGGG GCCCAAGGGA TTGTTTGTGC 300

TGCATTTGAT ACAGTTCTTG GGATAAATGT TGCAGTCAAG AAACTAAGCC GTCCTTTTCA 360

GAACCAAACT CATGCAAAGA GAGCTTATCG TGAACTTGTC CTCTTAAAAT GTGTCAATCA 420

TAAAAATATA ATTAGTTTGT TAAATGTGTT TACACCACAA AAAACTCTAG AAGAATTTCA 480

AGATGTGTAT TTGGTTATGG AATTAATGGA TGCTAACTTA TGTCAGGTTA TTCACATGGA 540

GCTGGATCAT GAAAGAATGT CCTACCTTCT TTACCAGATG CTTTGTGGTA TTAAACATCT 600

GCATTCAGCT GGTATAATTC ATAGAGATTT GAAGCCTAGC AACATTGTTG TGAAATCAGA 660

CTGCACCCTG AAGATCCTTG ACTTTGGCCT GGCCCGGACA GCGTGCACTA ACTTCATGAT 720

GACCCCTTAC GTGGTGACAC GGTACTACCG GGCGCCCGAA GTCATCCTGG GTATGGGCTA 780

CAAAGAGAAC GTGGATATCT GGTCAGTGGG TTGCATCATG GGAGAGCTGG TGAAAGGTTG 840

TGTGATATTC CAAGGCACTG ACCATATTGA TCAGTGGAAT AAAGTTATTG AGCAGCTGGG 900

AACACCATCA GCAGAGTTCA TGAAGAAACT TCAGCCAACT GTGAGGAATT ATGTCGAAAA 960

CAGACCAAAG TTTCCTGGAA TCAAATTGGA AGAACTCTTT CCAGATTGGT TATTCCCATC 1020

AGAATCTGAG CGAGACAAAA TAAAAACAAG TCAAGCCAGA GATCTGTTAT CACAAATGTT 1080

AGTGATTGAT CCTGACAAGC GGATCTCTGT AGACGAAGCT CTGCGTCACC CATACATCAC 1140

TGTTTGGTAT GACCCCGCCG AAGCAGAAGC CCCACCACCT CCAATTTATG ATGCCCAGTT 1200

GGAAGAAAGA GAACATGCAA TTGAGGAATG GAAAGAGCTA ATTTACAAAG AAGTCATGGA 1260

TTGGGAAGAA AGAAGCAAGA ATGGTGTTGT AAAAGATCAG CCTTCAGCAC AGATGCAGCA 1320

GTAAGTAGCA ACGCCACTCC TTCTCAGTCT TCATCGATCA ATGACATTTC ATCCATGTCC 1380

ACTGAGCAGA CGCTGGCCTC AGACACAGAC AGCAGTCTTG ATGCCTCGAC GGGACCCCCT 1440

GAAGGCTGTC GATGATAGGT TAGAAATAGC AAACCTGTCA GCATTGAAGG AACTCTCACC 1500

TCCGTGGGCC TGAAATGCTT GGGAGTTGAT GGAACCAAAT AGAAAAACTC CATGTTCTGC 1560

ATGTAAGAAA CACAATGCCT TGCCCTACTC AGACCTGATA GGATTGCCTG CTTAGATGAT 1620

AAAATGAGGC AGAATATGTC TGAAGGAAAA AATTCCAACC ACACTTCTAG AGATTTTGTC 1680

CAAGATCATT TCAGGTGAGC AGTTAGAGTA GGTGAATTTG TTTCCAAATT GTACTAGTGA 1740

CAGTTTCTCA TCATCTGTAA CTGTTGAGAT GTATGTGCAT GTGACCACCA ATGCTTGCTT 1800

GGACTTGCCC ATCTAGCACT TTGGGAATCA GTATTTAAAT GCCCAATAAT CTTCCAGGTA 1860

GTGCTGCTTC TGGAGTTATC TCCTAATCCT CCTAAGTAAT TTGGTGTCTG TCCAGGAAAA 1920

GTCGATTTAT GTGTATTAAT TGGCCATCAT GATGTTATCA TATCTTATTC CCCTTTATGC 1980

TATGATTTAT TCTATCTTTT GTATTTCAGG AGACATATAA TTAAATCTAT TTAATAAATA 2040

AAAATATATA GCTTTT 2056

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 503 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GAATTCTGCG GTCGCCACGA AGAGAACATG CATGATCTTC AGTACCATAC CCACTACGCC 60

CAGAACCGCA CTGTGGAGAG GTTTGAGTCT CTGGTAGGAC GCATGGCTTC TCACGAGATT 120

GAAATTGGCA CCATCTTCAC CAACATCAAT GCCACCGACA ACCACGCGCA CAGCATGCTC 180

ATGTACCTGG ATGACGTGCG GCTCTCCTGC ACGCTGGGCT TCCACACCCA TGCCGAGGAG 240

CTCTACTACC TGAACAAGTC TGTCTCCATC ATGCTGGGCA CCACAGACCT GCTCCGGGAG 300

CGCTTCAGCC TGCTCAGTGC CCGGCTGGAC CTCAACGTCC GGAACCTCTC CATGATCGTG 360

GAGGAGATGA AGGGAGGGGA CACACAGAAT GGGGAGATCC TTCGGAATGT AACATCCTAC 420

GAGGTGCCCC CGGCCTCCAG GACCAAGAGG TTCAAAAGAG ATTTGGCGTG AAACGGCTGT 480

GGCGGAGAGG CCAAAGGAGA CCG 503

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1618 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: -
(B) LOCATION: 58
(D) OTHER INFORMATION: /label= atg
/note= "start codon"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GAATTCTGCG GCCGCCGCCG CCACCCGAGC CGGAGCGGGT TGGGCCGCCA AGGCAAGATG 60

GTGGACTACA GCGTGTGGGA CCACATTGAG GTGTCTGATG ATGAAGACGA GACGCACCCC 120

AACATCGACA CGGCCAGTCT CTTCCGCTGG CGGCATCAGG CCCGGGTGGA ACGCATGGAG 180

CAGTTCCAGA AGGAGAAGGA GGAACTGGAC AGGGGCTGCC GCGAGTGCAA GCGCAAGGTG 240

GCCGAGTGCC AGAGGAAACT GAAGGAGCTG GAGGTGGCCG AGGGCGGCAA GGCAGAGCTG 300

GAGCGCCTGC AGGCCGAGAG CACAGCAGCT GCGCAAGGAG GAGCGGAGCT GGGAGCAGAA 360

GCTGGAGGGA GATGCGCAAG AAGGAGAAGA GCATGCCCTG GCAACGTGGA CACGCTCAGC 420

AAAGACGGCT TCAGCAAGAG CATGGTAAAT ACCAAGCCCG AGAAGACGGA GGAGGACTCA 480

GAGGAGGTGA GGGAGCAGAA ACACAAGACC TTCGTGGAAA AATACGAGAA ACAGATCAAG 540

CACTTTGGCA TGCTTCGCCG CTGGGATGAC AGCCACAAGT ACCTGTCAGA CAACGTCCAC 600

CTGGTGTGCG AGGAGACAGC CAATTACCTG GTCATTTGGT GCATTGACCT AGAGGTGGAG 660

GAGAAATGTG CACTCATGGA GCAGGTGGCC CACCAGACAA TCGTCATGCA ATTTATCCTG 720

GAGCTGGCCA AGAGCCTAAA GGTGGACCCC CGGGCCTGCT TCCGGCAGTT CTTCACTAAG 780

ATTAAGACAG CCGATCGCCA GTACATGGAG GGCTTCAACG ACGAGCTGGA AGCCTTCAAG 840

GAGCGTGTGC GGGGCCGTGC CAAGCTGCGC ATCGAGAAGG CCATGAAGGA GTACGAGGAG 900

GAGGAGCGCA AGAAGCGGCT CGGCCCCGGC GGCCTGGACC CCGTCGAGGT CTACGAGTCC 960

CTCCCTGAGG AACTCCAGAA GTGCTTCGAT GTGAAGGACG TGCAGATGCT GCAGGACGCC 1020

ATCAGCAAGA TGGACCCCAC CGACGCAAAG TACCACATGC AGCGCTGCAT TGACTCTGGC 1080

CTCTGGGTCC CCAACTCTAA GGCCAGCGAG GCCAAGGAGG GAGAGGAGGC AGGTCCTGGG 1140

GACCCATTAC TGGAAGCTGT TCCCAAGACG GGGCGATGAG AAGGATGTCA GTGTGTGACC 1200

TGCCCCAGCT ACCACCGCCA CCTGCTTCCA GGCCCCTATG TGCCCCCTTT TCAAGAAAAC 1260

AAGATAGATG CCATCTCGCC CGCTCCTGAC TTCCTCTACT TGCGCTGCTC GGCCCAGCCT 1320

GGGGGGCCCG CCCAGCCCTC CCTGGCCTCT CCACTGTCTC CACTCTCCAG CGCCCAATCA 1380

AGTCTCTGCT TTGAGTCAAG GGGCTTCACT GCCTGCAGCC CCCCATCAGC ATTATGCCAA 1440

AGGCCCGGGG GTCCGGGGAA GGGCAGAGGT CACCAGGCTG GTCTACCAGG TAGTTGGGGA 1500

GGGTCCCCAA CCAAGGGGCC GGCTCTCGTC ACTGGGCTCT GTTTTCACTG TTCGTCTGCT 1560

GTCTGTGTCT TCTAATTGGC AAACAACAAT GATCTTCCAA TAAAAGATTT CAGATGCC 1618

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 329 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GAATTCTGCG GCCGCGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG 60

AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG 120

AGAGAGAGAG AGAGAGAGAG AGAGAGAGAG AGTCTCTATG ATCTTTCCAT TCAAAACTTC 180

CAAGTTTCTC CTTATGTGGA ACCGAAATCT TTCTTTCTCC CGCGAAACTT TACTACTATC 240

AGATAATTGA AGACAGATCT CTGTGTGTTC TCTTCAAGCC CAAACCAATT CTGTTCCTTC 300

ACTCTATATA GTGGTAATAT GAATGTTTA 329

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 391 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
GAATTCGGCA CGAGGTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTGAAT GGGGTTATCC       60
AGGATGTGAC TTTTGGAGAT TGGTTTTTTC CGTGGATTAT CCTGCCCCTG AGATCCACCC      120
AAGTTGTGGG ATCTGAAACT TGCCCACCCT CCGGGATTTT GAAGGACGCT GAATCATGAG      180
CGACAGTAAT TGTGAAAGCC AGTTTTTTGG TGTGAAAGTG GAAGACTCAA CCTCCACTGT      240
CCTAAAACGT TACCAGAAGT TGAAACCAAT TGGCTCTGGG GCCCAAGGGA TTGTCGGGGC      300
TGCATCGGGT ACAGTTCTTG GGGATAAATG TTGGAGCCAA GGAATTAAGC CCGCCCCTTT      360
TCAGAACCCA ACTCATGAAA GGGAGTTCTC C                                     391
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 148 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Met Asp Thr Asp Thr Asp Thr Phe Thr Cys Gln Lys Asp Gly Arg Trp
1               5                   10                  15

Phe Pro Glu Arg Ile Ser Cys Ser Pro Lys Lys Cys Pro Leu Pro Glu
            20                  25                  30

Asn Ile Thr His Ile Leu Val His Gly Asp Asp Phe Ser Val Asn Arg
        35                  40                  45

Gln Val Ser Val Ser Cys Ala Glu Gly Tyr Thr Phe Glu Gly Val Asn
    50                  55                  60

Ile Ser Val Cys Gln Leu Asp Gly Thr Trp Glu Pro Pro Phe Ser Asp
65                  70                  75                  80

Glu Ser Cys Ser Pro Val Ser Cys Gly Lys Leu Ser Lys Val Gln Asn
                85                  90                  95

Met Asp Leu Trp Leu Ala Val Asn Thr Pro Leu Xaa Ser Thr Ile Ile
```

```
            100                      105                      110

Tyr Gln Cys Glu Pro Gly Tyr Glu Gly Gly Gly Glu Gln Gly Thr Cys
        115                     120                     125

Leu Pro Gly Glu Gln Thr Val Glu Trp Arg Gly Gly Asn Met Gln Arg
    130                     135                     140

Asp Gln Val Xaa
145
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 138 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Glu Leu Leu Ala Ala His Gly Thr Leu Glu Leu Gln Ala Glu Ile Leu
1               5                   10                  15

Pro Arg Arg Pro Pro Thr Pro Glu Ala Gln Ser Glu Glu Glu Arg Ser
            20                  25                  30

Asp Glu Glu Pro Glu Ala Lys Glu Glu Glu Glu Glu Lys Pro His Met
        35                  40                  45

Pro Thr Glu Phe Asp Phe Asp Asp Glu Pro Val Thr Pro Lys Asp Ser
    50                  55                  60

Leu Ile Asp Arg Arg Arg Thr Pro Gly Ser Ser Ala Arg Ser Gln Lys
65                  70                  75                  80

Arg Glu Ala Arg Leu Asp Lys Val Leu Ser Asp Met Lys Arg His Lys
                85                  90                  95

Lys Leu Glu Glu Gln Ile Leu Arg Thr Gly Arg Asp Leu Phe Ser Leu
            100                 105                 110

Asp Ser Glu Asp Pro Ser Pro Ala Ser Pro Pro Leu Arg Ser Ser Gly
        115                 120                 125

Ser Ser Leu Phe Pro Arg Gln Arg Lys Tyr
    130                 135
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 215 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Val Gly Thr Glu Glu Asp Gly Gly Gly Val Gly His Arg Thr Val Tyr
1               5                   10                  15

Leu Phe Asp Arg Arg Glu Lys Glu Ser Glu Leu Gly Asp Arg Pro Leu
            20                  25                  30

Gln Val Gly Glu Arg Ser Asp Tyr Ala Gly Phe Arg Ala Cys Val Cys
        35                  40                  45

Gln Thr Leu Gly Ile Ser Pro Glu Glu Lys Phe Val Ile Thr Thr Thr
    50                  55                  60

Ser Arg Lys Glu Ile Thr Cys Asp Asn Phe Asp Glu Thr Val Lys Asp
65                  70                  75                  80

Gly Val Thr Leu Tyr Leu Leu Gln Ser Val Asn Gln Leu Leu Leu Thr
                85                  90                  95

Ala Thr Lys Glu Arg Ile Asp Phe Leu Pro His Tyr Asp Thr Leu Val
            100                 105                 110

Lys Ser Gly Met Tyr Glu Tyr Tyr Ala Ser Glu Gly Gln Asn Pro Leu
        115                 120                 125

Pro Phe Ala Leu Ala Glu Leu Ile Asp Asn Ser Leu Ser Ala Thr Ser
    130                 135                 140

Arg Asn Ile Gly Val Arg Arg Ile Gln Ile Lys Leu Leu Phe Asp Glu
145                 150                 155                 160

Thr Gln Gly Lys Pro Ala Val Ala Val Ile Asp Asn Gly Arg Gly Met
                165                 170                 175

Thr Ser Lys Gln Leu Asn Asn Trp Ala Val Tyr Arg Leu Ser Lys Phe
            180                 185                 190

Thr Arg Gln Gly Asp Phe Glu Ser Asp His Ser Gly Cys Ser Ser Ser
        195                 200                 205

Thr Ser Ala Thr Gln Phe Lys
    210                 215
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
1               5                   10                  15

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
            20                  25                  30

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Ser Ile Arg Pro Asp
        35                  40                  45

Met Ser Arg Ser Val Ala Leu Asp Val Leu Ala Leu Leu Ser Leu Ser
    50                  55                  60

Cys Leu Glu Ala Ile Gln Val Ala Pro Ile Asp Ser
65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 94 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Leu Pro His Asn Phe Leu Thr Val Ala Pro Gly His Ser Ser His His
1               5                   10                  15

Ser Pro Gly Leu Gln Gly Gln Gly Val Thr Leu Pro Gly Glu Pro Pro
            20                  25                  30

Leu Pro Glu Lys Lys Arg Val Ser Glu Gly Asp Arg Ser Leu Val Ser
        35                  40                  45

Val Ser Pro Ser Ser Ser Gly Phe Ser Ser Pro His Ser Gly Ser Asn
    50                  55                  60

Ile Ser Ile Pro Phe Pro Tyr Val Leu Pro Asp Phe Ser Lys Ala Ser
65                  70                  75                  80

Glu Gly Gly Ser Thr Leu Gln Ile Val Gln Val Ile Asn Leu
                85                  90
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 135 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Arg Arg Pro Pro Ala Asp Arg Gly Arg Ser Pro Pro Gly Gly Pro Gly
1               5                   10                  15

Ser Arg Thr Gly Glu Pro Gly Arg Glu Ser Ser Ala Ala Gly Cys Thr
            20                  25                  30

Ala Ala Ala Pro Arg Glu Gly Cys Ser Gly Gln Arg Pro Pro Leu Leu
        35                  40                  45

Arg Ala Asp Ser Ala Gly Leu Gly Arg Cys Gly Gly Leu Cys Arg Pro
    50                  55                  60

Pro Val Ser Thr Tyr Cys Trp Arg Arg Phe Ala Pro Arg Pro Ala Glu
65                  70                  75                  80

Trp Gly Gly Gly Pro Gly Arg Arg Thr Gly Gly Phe Ala Val Phe Leu
                85                  90                  95

Gln Pro Pro Ile Leu Leu Ser Ser Pro Thr Ala Leu Gln Pro Ser Phe
            100                 105                 110

Asp Asn Leu Arg Cys Leu Pro Ser Ser Ile His Cys Phe Gly Lys Gln
        115                 120                 125

Pro Pro Ile Pro Pro Leu Leu
    130                 135
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 937 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Met Leu Ala Ala Ala Gly Gly Arg Val Pro Thr Ala Ala Gly Ala Trp
1               5                   10                  15

Leu Leu Arg Gly Gln Arg Thr Cys Asp Ala Ser Pro Pro Trp Ala Leu
            20                  25                  30

Trp Gly Arg Gly Pro Ala Ile Gly Gly Gln Trp Arg Gly Phe Trp Glu
        35                  40                  45

Ala Ser Ser Arg Gly Gly Gly Ala Phe Ser Gly Gly Glu Asp Ala Ser
    50                  55                  60

Glu Gly Gly Ala Glu Glu Gly Ala Gly Gly Ala Gly Gly Ser Ala Gly
65                  70                  75                  80

Ala Gly Glu Gly Pro Val Ile Thr Ala Leu Thr Pro Met Thr Ile Pro
                85                  90                  95

Asp Val Phe Pro His Leu Pro Leu Ile Ala Ile Thr Arg Asn Pro Val
            100                 105                 110

Phe Pro Arg Phe Ile Lys Ile Ile Glu Val Lys Asn Lys Lys Leu Val
        115                 120                 125

Glu Leu Leu Arg Arg Lys Val Arg Leu Ala Gln Pro Tyr Val Gly Val
    130                 135                 140

Phe Leu Lys Arg Asp Asp Ser Asn Glu Ser Asp Val Val Glu Ser Leu
145                 150                 155                 160

Asp Glu Ile Tyr His Thr Gly Thr Phe Ala Gln Ile His Glu Met Gln
                165                 170                 175

Asp Leu Gly Asp Lys Leu Arg Met Ile Val Met Gly His Arg Arg Val
            180                 185                 190

His Ile Ser Arg Gln Leu Glu Val Glu Pro Glu Glu Pro Glu Ala Glu
        195                 200                 205

Asn Lys His Lys Pro Arg Arg Lys Ser Lys Arg Gly Lys Lys Glu Ala
    210                 215                 220

Glu Asp Glu Leu Ser Ala Arg His Pro Ala Glu Leu Ala Met Glu Pro
225                 230                 235                 240

Thr Pro Glu Leu Pro Ala Glu Val Leu Met Val Glu Val Glu Asn Val
                245                 250                 255

Val His Glu Asp Phe Gln Val Thr Glu Glu Val Lys Ala Leu Thr Ala
            260                 265                 270

Glu Ile Val Lys Thr Ile Arg Asp Ile Ile Ala Leu Asn Pro Leu Tyr
        275                 280                 285

Arg Glu Ser Val Leu Gln Met Met Gln Ala Gly Gln Arg Val Val Asp
    290                 295                 300
```

Asn Pro Ile Tyr Leu Ser Asp Met Gly Ala Ala Leu Thr Gly Ala Glu
305 310 315 320

Ser His Glu Leu Gln Asp Val Leu Glu Glu Thr Asn Ile Pro Lys Arg
325 330 335

Leu Tyr Lys Ala Leu Ser Leu Leu Lys Lys Glu Phe Glu Leu Ser Lys
340 345 350

Leu Gln Gln Arg Leu Gly Arg Glu Val Glu Glu Lys Ile Lys Gln Thr
355 360 365

His Arg Lys Tyr Leu Leu Gln Glu Gln Leu Lys Ile Ile Lys Lys Glu
370 375 380

Leu Gly Leu Glu Lys Asp Asp Lys Asp Ala Ile Glu Glu Lys Phe Arg
385 390 395 400

Glu Arg Leu Lys Glu Leu Val Val Pro Lys His Val Met Asp Val Val
405 410 415

Asp Glu Glu Leu Ser Lys Leu Gly Leu Leu Asp Asn His Ser Ser Glu
420 425 430

Phe Asn Val Thr Arg Asn Tyr Leu Asp Trp Leu Thr Ser Ile Pro Trp
435 440 445

Gly Lys Tyr Ser Asn Glu Asn Leu Asp Leu Ala Arg Ala Gln Ala Val
450 455 460

Leu Glu Glu Asp His Tyr Gly Met Glu Asp Val Lys Lys Arg Ile Leu
465 470 475 480

Glu Phe Ile Ala Val Ser Gln Leu Arg Gly Ser Thr Gln Gly Lys Ile
485 490 495

Leu Cys Phe Tyr Gly Pro Pro Gly Val Gly Lys Thr Ser Ile Ala Arg
500 505 510

Ser Ile Ala Arg Ala Leu Asn Arg Glu Tyr Phe Arg Phe Ser Val Gly
515 520 525

Gly Met Thr Asp Val Ala Glu Ile Lys Gly His Arg Arg Thr Tyr Val
530 535 540

Gly Ala Met Pro Gly Lys Ile Ile Gln Cys Leu Lys Lys Thr Lys Thr
545 550 555 560

Glu Asn Pro Leu Ile Leu Ile Asp Glu Val Asp Lys Ile Gly Arg Gly
565 570 575

Tyr Gln Gly Asp Pro Ser Ser Ala Leu Leu Glu Leu Leu Asp Pro Glu
580 585 590

Gln Asn Ala Asn Phe Leu Asp His Tyr Leu Asp Val Pro Val Asp Leu
595 600 605

Ser Lys Val Leu Phe Ile Cys Thr Ala Asn Val Thr Asp Thr Ile Pro

610 615 620

Glu Pro Leu Arg Asp Arg Met Glu Met Ile Asn Val Ser Gly Tyr Val
625 630 635 640

Ala Gln Glu Lys Leu Ala Ile Ala Glu Arg Tyr Leu Val Pro Gln Ala
645 650 655

Arg Ala Leu Cys Gly Leu Asp Glu Ser Lys Ala Lys Leu Ser Ser Asp
660 665 670

Val Leu Thr Leu Leu Ile Lys Gln Tyr Cys Arg Glu Ser Gly Val Arg
675 680 685

Asn Leu Gln Lys Gln Val Glu Lys Val Leu Arg Lys Ser Ala Tyr Lys
690 695 700

Ile Val Ser Gly Glu Ala Glu Ser Val Glu Val Thr Pro Glu Asn Leu
705 710 715 720

Gln Asp Phe Val Gly Lys Pro Val Phe Thr Val Glu Arg Met Tyr Asp
725 730 735

Val Thr Pro Pro Gly Val Val Met Gly Leu Ala Trp Thr Ala Met Gly
740 745 750

Gly Ser Thr Leu Phe Val Glu Thr Ser Leu Arg Arg Pro Gln Asp Lys
755 760 765

Asp Ala Lys Gly Asp Lys Asp Gly Ser Leu Glu Val Thr Gly Gln Leu
770 775 780

Gly Glu Val Met Lys Glu Ser Ala Arg Ile Ala Tyr Thr Phe Ala Arg
785 790 795 800

Ala Phe Leu Met Gln His Ala Pro Ala Asn Asp Tyr Leu Val Thr Ser
805 810 815

His Ile His Leu His Val Pro Glu Gly Ala Thr Pro Lys Asp Gly Pro
820 825 830

Ser Ala Gly Cys Thr Ile Val Thr Ala Leu Leu Ser Leu Ala Met Gly
835 840 845

Arg Pro Val Arg Gln Asn Leu Ala Met Thr Gly Glu Val Ser Leu Thr
850 855 860

Gly Lys Ile Leu Pro Val Gly Gly Ile Lys Glu Lys Thr Ile Ala Ala
865 870 875 880

Lys Arg Ala Gly Val Thr Cys Ile Ile Leu Pro Ala Glu Asn Lys Lys
885 890 895

Asp Phe Tyr Asp Leu Ala Ala Phe Ile Thr Glu Gly Leu Glu Val His
900 905 910

Phe Val Glu His Tyr Arg Glu Ile Phe Asp Ile Ala Phe Pro Asp Glu
915 920 925

Gln Ala Glu Ala Leu Ala Val Glu Arg
    930   935

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 129 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Thr Gly Glu Pro Cys Cys Asp Trp Val Gly Asp Glu Gly Ala Gly His
1               5                   10                  15

Phe Val Lys Met Val His Asn Gly Ile Glu Tyr Gly Asp Met Gln Leu
            20                  25                  30

Ile Cys Glu Ala Tyr His Leu Met Lys Asp Val Leu Gly Met Ala Gln
        35                  40                  45

Asp Glu Met Ala Gln Ala Phe Glu Asp Trp Asn Lys Thr Glu Leu Asp
    50                  55                  60

Ser Phe Leu Ile Glu Ile Thr Ala Asn Ile Leu Lys Phe Gln Asp Thr
65                  70                  75                  80

Asp Gly Lys His Leu Leu Pro Lys Ile Xaa Asp Ser Ala Gly Gln Lys
                85                  90                  95

Gly Thr Gly Lys Trp Thr Ala Ile Phe Ala Leu Gly Leu Arg Gly Thr
            100                 105                 110

Arg His Pro His Trp Gly Arg Cys Leu Xaa Ser Val Leu Ile Ile Ser
        115                 120                 125

Xaa
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 376 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
Met Asp Met Val Glu Asn Ala Asp Ser Leu Gln Ala Gln Glu Arg Lys
1               5                   10                  15

Asp Ile Leu Met Lys Tyr Asp Lys Gly His Arg Ala Gly Leu Pro Glu
            20                  25                  30

Asp Lys Gly Pro Glu Pro Val Gly Ile Asn Ser Ser Ile Asp Arg Phe
        35                  40                  45

Gly Ile Leu His Glu Thr Glu Leu Pro Pro Val Thr Ala Arg Glu Ala
    50                  55                  60

Lys Lys Ile Arg Arg Glu Met Thr Arg Thr Ser Lys Trp Met Glu Met
65                  70                  75                  80

Leu Gly Glu Trp Glu Thr Tyr Lys His Ser Ser Lys Leu Ile Asp Arg
                85                  90                  95

Val Tyr Lys Gly Ile Pro Met Asn Ile Arg Gly Pro Val Trp Ser Val
            100                 105                 110

Leu Leu Asn Ile Gln Glu Ile Lys Leu Lys Asn Pro Gly Arg Tyr Gln
        115                 120                 125

Ile Met Lys Glu Arg Gly Lys Arg Ser Ser Glu His Ile His His Ile
    130                 135                 140

Asp Leu Asp Val Arg Thr Thr Leu Arg Asn His Val Phe Phe Arg Asp
145                 150                 155                 160

Arg Tyr Gly Ala Lys Gln Arg Glu Leu Phe Tyr Ile Leu Leu Ala Tyr
                165                 170                 175

Ser Glu Tyr Asn Pro Glu Val Gly Tyr Cys Arg Asp Leu Ser His Ile
            180                 185                 190

Thr Ala Leu Phe Leu Leu Tyr Leu Pro Glu Glu Asp Ala Phe Trp Ala
        195                 200                 205

Leu Val Gln Leu Leu Ala Ser Glu Arg His Ser Leu Pro Gly Phe His
    210                 215                 220

Ser Pro Asn Gly Gly Thr Val Gln Gly Leu Gln Asp Gln Gln Glu His
225                 230                 235                 240

Val Val Pro Lys Ser Gln Pro Lys Thr Met Trp His Gln Asp Lys Glu
                245                 250                 255

Gly Leu Cys Gly Gln Cys Ala Ser Leu Gly Cys Leu Leu Arg Asn Leu
            260                 265                 270

Ile Asp Gly Ile Ser Leu Gly Leu Thr Leu Arg Leu Trp Asp Val Tyr
        275                 280                 285

Leu Val Glu Gly Glu Gln Val Leu Met Pro Ile Thr Ser Ile Ala Leu
```

```
    290                 295                 300

Lys Val Gln Gln Lys Arg Leu Met Lys Thr Ser Arg Cys Gly Leu Trp
305                 310                 315                 320

Ala Arg Leu Arg Asn Gln Phe Phe Asp Thr Trp Ala Met Asn Asp Asp
                325                 330                 335

Thr Val Leu Lys His Leu Arg Ala Ser Thr Lys Lys Leu Thr Arg Lys
            340                 345                 350

Gln Gly Asp Leu Pro Pro Pro Gly Pro Thr Ala Leu Gly Arg Arg Cys
        355                 360                 365

Val Ala Gly Ser Pro Gln Pro Val
    370                 375
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 315 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
Glu Phe Cys Gly Arg Gln Lys Ile His Lys Glu Met Pro Cys Lys Cys
1               5                   10                  15

Thr Val Cys Gly Ser Asp Phe Cys His Thr Ser Tyr Leu Leu Glu His
            20                  25                  30

Gln Arg Val His His Glu Glu Lys Ala Tyr Glu Tyr Asp Glu Tyr Gly
        35                  40                  45

Leu Ala Tyr Ile Lys Gln Gln Gly Ile His Phe Arg Glu Lys Pro Tyr
    50                  55                  60

Thr Cys Ser Glu Cys Gly Lys Asp Phe Arg Leu Asn Ser His Leu Ile
65                  70                  75                  80

Gln His Gln Arg Ile His Thr Gly Glu Lys Ala His Glu Cys His Glu
                85                  90                  95

Cys Gly Lys Ala Phe Ser Gln Thr Ser Cys Leu Ile Gln His His Lys
            100                 105                 110

Met His Arg Lys Glu Thr Arg Ile Glu Cys Asn Glu Tyr Xaa Gly Gln
        115                 120                 125

Val Gln Val Ile Ala Gln Ile Leu Ser Cys Asn Lys Glu Val Leu Thr
    130                 135                 140
```

Arg Gln Lys Ala Phe Asp Trp Xaa Cys Met Gly Lys Glu Leu Gln Ser
145 150 155 160

Glu Ser Thr Ser Ser Ser Thr Ser Glu His Ser Tyr Gln Arg Glu Leu
165 170 175

Met Asn Val Met Lys Met Gly Arg Tyr Leu Ser Asn Ser Gly Phe Ile
180 185 190

Gln His Leu Arg Val His Thr Arg Glu Gln Ile Met Tyr Val Leu His
195 200 205

Val Val Lys Pro Ser Val Ile Ala Gln Pro Leu Leu Ser Ile Arg Xaa
210 215 220

Phe Thr Pro Glu Arg Asn Pro Leu Asn Val Thr Asn Glu Glu Lys Val
225 230 235 240

Leu Val Leu Asn Ser Xaa Ser Thr Pro Ala Asn Leu Tyr Gln Xaa Glu
245 250 255

Ile Leu Gln Met Tyr Trp Ile Val Ala Asn Phe Ser Cys Tyr Xaa Tyr
260 265 270

Phe His Thr Leu Val Thr Cys Gly Gly Ile His Met Gly Ile Asn Ser
275 280 285

His Cys Cys Asn Asp Cys Glu Lys His Gln Ala Arg Asn Phe Leu Val
290 295 300

Arg Phe Asn Ser Thr Pro Cys Lys Arg Phe Leu
305 310 315

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 127 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Leu Phe Ala Glu Ala Gly Pro Asp Phe Glu Leu Arg Leu Glu Leu Tyr
1 5 10 15

Gly Ala Cys Val Glu Glu Glu Gly Ala Leu Thr Gly Gly Pro Lys Arg
20 25 30

Leu Ala Thr Lys Leu Ser Ser Ser Leu Gly Arg Ser Ser Gly Arg Arg
35 40 45

Val Arg Ala Ser Leu Asp Ser Ala Gly Gly Ser Gly Ser Ser Pro Ile
50 55 60

Leu Leu Pro Thr Pro Val Val Gly Gly Pro Arg Tyr His Leu Leu Ala
65 70 75 80

His Thr Thr Leu Thr Leu Gly Gly Val Gln Asp Gly Phe Arg Thr His
85 90 95

Asp Leu Thr Leu Gly Ser His Glu Glu Asn Leu Pro Gly Cys Pro Phe
100 105 110

Met Val Ala Cys Val Ala Val Trp Gln Leu Ser Leu Ser Ala Xaa
115 120 125

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 278 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

His Glu Ser Lys Gln Glu Lys Glu Lys Ser Lys Lys Lys Lys Gly Gly
1 5 10 15

Lys Thr Glu Gln Asp Gly Tyr Gln Lys Pro Thr Asn Lys His Phe Thr
20 25 30

Gln Ser Pro Lys Glu Val Ser Gly Arg Pro Ala Gly Val Leu Trp Lys
35 40 45

Ala Asn Glu Gly Leu Leu Leu Ile Thr Ala Pro Lys Ala Glu Glu Gln
50 55 60

Gln Arg Asp Glu Tyr Leu Glu Ser Phe Cys Lys Met Ala Thr Arg Lys
65 70 75 80

Ile Ser Val Ile Thr Ile Phe Gly Pro Val Asn Asn Ser Thr Met Lys
85 90 95

Ile Asp His Phe Gln Leu Asp Asn Glu Lys Pro Met Arg Val Val Asp
100 105 110

Asp Glu Asp Leu Val Asp Gln Arg Leu Ile Ser Glu Leu Arg Lys Glu
115 120 125

Tyr Gly Met Thr Tyr Asn Asp Phe Phe Met Val Leu Thr Asp Val Asp
130 135 140

Leu Arg Val Lys Gln Tyr Tyr Glu Val Pro Ile Thr Met Lys Ser Val

145 150 155 160

Leu Asp Leu Ile Asp Thr Phe Gln Ser Arg Ile Lys Asp Met Glu Lys
165 170 175

Gln Lys Lys Glu Gly Ile Val Cys Lys Glu Asp Lys Lys Gln Ser Leu
180 185 190

Glu Asn Phe Leu Ser Arg Phe Arg Trp Arg Arg Arg Leu Leu Val Ile
195 200 205

Ser Ala Pro Asn Asp Glu Asp Trp Ala Tyr Ser Gln Gln Leu Ser Ala
210 215 220

Leu Ser Gly Gln Ala Cys Asn Phe Gly Leu Arg His Ile Thr Ile Leu
225 230 235 240

Lys Leu Leu Gly Val Gly Glu Glu Val Gly Gly Val Leu Glu Leu Phe
245 250 255

Pro Ile Asn Gly Ser Ser Val Val Glu Arg Glu Asp Val Pro Ala His
260 265 270

Leu Gly Glu Arg His Pro
275

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 292 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

His Tyr Ser Cys Asn Ile Ser Gly Ser Leu Lys Arg His Tyr Asn Arg
1 5 10 15

Lys His Pro Asn Glu Glu Tyr Ala Asn Val Gly Thr Gly Glu Leu Ala
20 25 30

Ala Glu Val Leu Ile Gln Gln Gly Gly Leu Lys Cys Pro Val Cys Ser
35 40 45

Phe Val Tyr Gly Thr Lys Trp Glu Phe Asn Arg His Leu Lys Asn Lys
50 55 60

His Gly Leu Lys Val Val Glu Ile Asp Gly Asp Pro Lys Trp Glu Thr
65 70 75 80

Ala Thr Glu Ala Pro Glu Glu Pro Ser Thr Gln Tyr Leu His Ile Thr

```
                    85                  90                  95

Glu Ser Glu Glu Asp Val Gln Gly Thr Gln Ala Ala Val Ala Ala Leu
            100                 105                 110

Gln Asp Leu Arg Tyr Thr Ser Glu Ser Gly Asp Arg Leu Asp Pro Thr
        115                 120                 125

Ala Val Asn Ile Leu Gln Gln Ile Ile Glu Leu Gly Ala Glu Thr His
    130                 135                 140

Asp Ala Thr Ala Leu Ala Ser Val Val Ala Met Ala Pro Gly Thr Val
145                 150                 155                 160

Thr Val Val Lys Gln Val Thr Glu Glu Glu Pro Ser Ser Asn His Thr
                165                 170                 175

Val Met Ile Gln Glu Thr Val Gln Gln Ala Ser Val Glu Leu Ala Glu
            180                 185                 190

Gln His His Leu Val Val Ser Ser Asp Asp Val Glu Gly Ile Glu Thr
        195                 200                 205

Val Thr Val Tyr Thr Gln Gly Gly Glu Ala Ser Glu Phe Ile Val Tyr
    210                 215                 220

Val Gln Glu Ala Met Gln Pro Val Glu Glu Gln Ala Cys Gly Ala Ala
225                 230                 235                 240

Gly Pro Gly Thr Leu Glu Asp Met Trp His Arg Met Ala Thr Gly Arg
                245                 250                 255

Gly Cys Pro Gly Ser Ser Gly Thr Gln Gly Gly Glu Ala Thr Phe Leu
            260                 265                 270

Pro Tyr Pro Arg Met Val Ser Pro Leu Pro Ser Leu Pro Ser Ser Leu
        275                 280                 285

Ile Gly Leu Ser
    290
```

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 83 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

```
Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
```

```
1               5                   10                  15

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
            20                  25                  30

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
        35                  40                  45

Glu Arg Glu Arg Glu Ser Pro Gly Leu Asn Thr Tyr Gly Thr Asp Val
    50                  55                  60

Ile Ser Thr Ser Pro Phe Ile Glu Ser Val Ile Tyr Leu Glu Trp Arg
65                  70                  75                  80

His Arg Phe
```

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 191 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```
Glu Phe Cys Gly Arg Arg Ser Glu Val Leu Leu Val Ser Glu Asp Gly
1               5                   10                  15

Lys Ile Leu Ala Glu Ala Asp Gly Leu Ser Thr Asn His Trp Leu Ile
            20                  25                  30

Gly Thr Asp Lys Cys Val Glu Arg Ile Asn Glu Met Val Asn Arg Ala
        35                  40                  45

Lys Arg Lys Ala Gly Val Asp Pro Leu Val Pro Leu Arg Ser Leu Gly
    50                  55                  60

Leu Ser Leu Ser Gly Gly Asp Gln Glu Asp Ala Gly Arg Ile Leu Ile
65                  70                  75                  80

Glu Glu Leu Arg Asp Arg Phe Pro Tyr Leu Ser Glu Ser Tyr Leu Ile
                85                  90                  95

Thr Thr Asp Ala Ala Gly Ser Ile Asp Thr Ala Thr Pro Asp Gly Gly
            100                 105                 110

Val Val Leu Ile Ser Gly Thr Gly Ser Asn Cys Arg Leu Ile Asn Pro
        115                 120                 125

Asp Gly Ser Glu Ser Gly Cys Gly Arg Leu Gly Gly Ile Leu Trp Val
    130                 135                 140
```

Met Arg Val Gln Pro Thr Gly Ser His Thr Lys Gln Xaa Lys Xaa Cys
145 150 155 160

Leu Asp Ser Ile Glu Asn Xaa Arg Arg Ser His Asp Ile Gly Tyr Val
165 170 175

Lys Gln Ala Met Phe His Tyr Phe Gln Val Gln Ile Arg Xaa Val
180 185 190

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Gln Ser Ser Thr Glu Ile Ser Lys Thr Arg Gly Gly Glu Thr Lys Arg
1 5 10 15

Glu Val Arg Val Glu Glu Ser Thr Gln Val Gly Gly Ala Pro Leu Pro
20 25 30

Cys Cys Val Trp Gly Leu Pro Gly Pro Gly Ala Pro Gly Ile Leu Arg
35 40 45

Gln Tyr His Pro Ala Ala Gly Gly
50 55

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 93 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Gly Glu Glu Lys Arg Val Ser Arg Glu Pro Ala Gly Val Leu Ser Gln
1 5 10 15

Ser Gly Met Gln Leu Glu Tyr Leu Ser Leu Pro Phe Gln Leu Pro Ala
20 25 30

```
Arg Arg Ser Leu Gln Val Glu Leu Cys Gly Gly Gln Pro Val Leu Ser
        35                  40                  45

Arg Val Lys Val Gln Trp Arg Pro Ser Gly Ser Thr Pro Asn Val Ile
    50                  55                  60

Glu Gly Asp Leu Leu Val Phe Gly Gln Gln Leu Ala Pro Pro Met Gly
65                  70                  75                  80

Met Gly Glu Val Met Glu Glu Glu Arg Arg Leu Cys Xaa
                85                  90
```

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 84 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```
Ala Leu His Val Asn Asn Asp Arg Ala Lys Val Ile Leu Lys Pro Asp
1               5                   10                  15

Lys Thr Thr Ile Thr Glu Pro His His Ile Trp Pro Thr Leu Thr Asp
            20                  25                  30

Glu Glu Trp Ile Lys Val Glu Val Gln Leu Lys Asp Leu Ile Leu Ala
        35                  40                  45

Asp Tyr Gly Lys Lys Asn Asn Val Asn Val Ala Ser Leu Thr Gln Ser
    50                  55                  60

Glu Ile Arg Asp Ile Ile Leu Gly Ile Glu Asp Leu Arg Glu Pro Ser
65                  70                  75                  80

Gln Glu Gly Glu
```

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 382 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Met Ser Asp Ser Lys Cys Asp Ser Gln Phe Tyr Ser Val Gln Val Ala
1 5 10 15

Asp Ser Thr Phe Thr Val Leu Lys Arg Tyr Gln Gln Leu Lys Pro Ile
20 25 30

Gly Ser Gly Ala Gln Gly Ile Val Cys Ala Ala Phe Asp Thr Val Leu
35 40 45

Gly Ile Asn Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Asn Gln
50 55 60

Thr His Ala Lys Arg Ala Tyr Arg Glu Leu Val Leu Leu Lys Cys Val
65 70 75 80

Asn His Lys Asn Ile Ile Ser Leu Leu Asn Val Phe Thr Pro Gln Lys
85 90 95

Thr Leu Glu Glu Phe Gln Asp Val Tyr Leu Val Met Glu Leu Met Asp
100 105 110

Ala Asn Leu Cys Gln Val Ile His Met Glu Leu Asp His Glu Arg Met
115 120 125

Ser Tyr Leu Leu Tyr Gln Met Leu Cys Gly Ile Lys His Leu His Ser
130 135 140

Ala Gly Ile Ile His Arg Asp Leu Lys Pro Ser Asn Ile Val Val Lys
145 150 155 160

Ser Asp Cys Thr Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg Thr Ala
165 170 175

Cys Thr Asn Phe Met Met Thr Pro Tyr Val Val Thr Arg Tyr Tyr Arg
180 185 190

Ala Pro Glu Val Ile Leu Gly Met Gly Tyr Lys Glu Asn Val Asp Ile
195 200 205

Trp Ser Val Gly Cys Ile Met Gly Glu Leu Val Lys Gly Cys Val Ile
210 215 220

Phe Gln Gly Thr Asp His Ile Asp Gln Trp Asn Lys Val Ile Glu Gln
225 230 235 240

Leu Gly Thr Pro Ser Ala Glu Phe Met Lys Lys Leu Gln Pro Thr Val
245 250 255

Arg Asn Tyr Val Glu Asn Arg Pro Lys Phe Pro Gly Ile Lys Leu Glu
260 265 270

Glu Leu Phe Pro Asp Trp Leu Phe Pro Ser Glu Ser Glu Arg Asp Lys
275 280 285

Ile Lys Thr Ser Gln Ala Arg Asp Leu Leu Ser Gln Met Leu Val Ile
290 295 300

```
Asp Pro Asp Lys Arg Ile Ser Val Asp Glu Ala Leu Arg His Pro Tyr
305                 310                 315                 320

Ile Thr Val Trp Tyr Asp Pro Ala Glu Ala Glu Ala Pro Pro Pro Pro
                325                 330                 335

Ile Tyr Asp Ala Gln Leu Glu Glu Arg Glu His Ala Ile Glu Glu Trp
            340                 345                 350

Lys Glu Leu Ile Tyr Lys Glu Val Met Asp Trp Glu Glu Arg Ser Lys
        355                 360                 365

Asn Gly Val Val Lys Asp Gln Pro Ser Ala Gln Met Gln Gln
    370                 375                 380
```

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

```
His Glu Glu Asn Met His Asp Leu Gln Tyr His Thr His Tyr Ala Gln
1               5                   10                  15

Asn Arg Thr Val Glu Arg Phe Glu Ser Leu Val Gly Arg Met Ala Ser
            20                  25                  30

His Glu Ile Glu Ile Gly Thr Ile Phe Thr Asn Ile Asn Ala Thr Asp
        35                  40                  45

Asn His Ala His Ser Met Leu Met Tyr Leu Asp Asp Val Arg Leu Ser
    50                  55                  60

Cys Thr Leu Gly Phe His Thr His Ala Glu Glu Leu Tyr Tyr Leu Asn
65                  70                  75                  80

Lys Ser Val Ser Ile Met Leu Gly Thr Thr Asp Leu Leu Arg Glu Arg
                85                  90                  95

Phe Ser Leu Leu Ser Ala Arg Leu Asp Leu Asn Val Arg Asn Leu Ser
            100                 105                 110

Met Ile Val Glu Glu Met Lys Gly Gly Asp Thr Gln Asn Gly Glu Ile
        115                 120                 125

Leu Arg Asn Val Thr Ser Tyr Glu Val Pro Pro Ala Ser Arg Thr Lys
    130                 135                 140
```

Arg Phe Lys Arg Asp Leu Ala
145 150

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 373 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Met Val Asp Tyr Ser Val Trp Asp His Ile Glu Val Ser Asp Asp Glu
1 5 10 15

Asp Glu Thr His Pro Asn Ile Asp Thr Ala Ser Leu Phe Arg Trp Arg
20 25 30

His Gln Ala Arg Val Glu Arg Met Glu Gln Phe Gln Lys Glu Lys Glu
35 40 45

Glu Leu Asp Arg Gly Cys Arg Glu Cys Lys Arg Lys Val Ala Glu Cys
50 55 60

Gln Arg Lys Leu Lys Glu Leu Glu Val Ala Glu Gly Gly Lys Ala Glu
65 70 75 80

Leu Glu Arg Leu Gln Ala Glu Ser Thr Ala Ala Ala Gln Gly Gly Ala
85 90 95

Glu Leu Gly Ala Glu Ala Gly Gly Arg Cys Ala Arg Arg Arg Arg Ala
100 105 110

Cys Pro Gly Asn Val Asp Thr Leu Ser Lys Asp Gly Phe Ser Lys Ser
115 120 125

Met Val Asn Thr Lys Pro Glu Lys Thr Glu Glu Asp Ser Glu Glu Val
130 135 140

Arg Glu Gln Lys His Lys Thr Phe Val Glu Lys Tyr Glu Lys Gln Ile
145 150 155 160

Lys His Phe Gly Met Leu Arg Arg Trp Asp Asp Ser His Lys Tyr Leu
165 170 175

Ser Asp Asn Val His Leu Val Cys Glu Glu Thr Ala Asn Tyr Leu Val
180 185 190

Ile Trp Cys Ile Asp Leu Glu Val Glu Glu Lys Cys Ala Leu Met Glu
195 200 205

Gln Val Ala His Gln Thr Ile Val Met Gln Phe Ile Leu Glu Leu Ala
210 215 220

Lys Ser Leu Lys Val Asp Pro Arg Ala Cys Phe Arg Gln Phe Phe Thr
225 230 235 240

Lys Ile Lys Thr Ala Asp Arg Gln Tyr Met Glu Gly Phe Asn Asp Glu
245 250 255

Leu Glu Ala Phe Lys Glu Arg Val Arg Gly Arg Ala Lys Leu Arg Ile
260 265 270

Glu Lys Ala Met Lys Glu Tyr Glu Glu Glu Glu Arg Lys Lys Arg Leu
275 280 285

Gly Pro Gly Gly Leu Asp Pro Val Glu Val Tyr Glu Ser Leu Pro Glu
290 295 300

Glu Leu Gln Lys Cys Phe Asp Val Lys Asp Val Gln Met Leu Gln Asp
305 310 315 320

Ala Ile Ser Lys Met Asp Pro Thr Asp Ala Lys Tyr His Met Gln Arg
325 330 335

Cys Ile Asp Ser Gly Leu Trp Val Pro Asn Ser Lys Ala Ser Glu Ala
340 345 350

Lys Glu Gly Glu Glu Ala Gly Pro Gly Asp Pro Leu Leu Glu Ala Val
355 360 365

Pro Lys Thr Gly Arg
370

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 143 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Arg Arg His Pro Ser Arg Ser Gly Leu Gly Arg Gln Gly Lys Met Val
1 5 10 15

Asp Tyr Ser Val Trp Asp His Ile Glu Val Ser Asp Asp Glu Asp Glu
20 25 30

Thr His Pro Asn Ile Asp Thr Ala Ser Leu Phe Arg Trp Arg His Gln
35 40 45

Ala Arg Val Glu Arg Met Glu Gln Phe Gln Lys Glu Lys Glu Glu Leu
50 55 60

Asp Ser Gly Cys Arg Glu Cys Lys Arg Lys Val Ala Glu Cys Gln Arg
65 70 75 80

Lys Leu Lys Glu Leu Glu Val Ala Glu Gly Gly Lys Ala Glu Leu Glu
85 90 95

Arg Leu Gln Ala Glu Ala Gln Gln Leu Arg Asn Glu Glu Arg Ser Trp
100 105 110

Glu Gln Lys Leu Glu Glu Met Arg Lys Lys Glu Lys Ser Met Pro Trp
115 120 125

Gln Arg Gly His Ala Gln Gln Arg Arg Leu Gln Gln Arg Ala Trp
130 135 140

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 77 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
1 5 10 15

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg
20 25 30

Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Arg Glu Ser Leu Tyr
35 40 45

Asp Leu Ser Ile Gln Asn Phe Gln Val Ser Pro Tyr Val Glu Pro Lys
50 55 60

Ser Phe Phe Leu Pro Arg Asn Phe Thr Thr Ile Arg Xaa
65 70 75

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 72 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Met Ser Asp Ser Asn Cys Glu Ser Gln Phe Phe Gly Val Lys Val Glu
1               5                   10                  15

Asp Ser Thr Ser Thr Val Leu Lys Arg Tyr Gln Lys Leu Lys Pro Ile
            20                  25                  30

Gly Ser Gly Ala Gln Gly Ile Val Gly Ala Ala Ser Gly Thr Val Leu
        35                  40                  45

Gly Asp Lys Cys Trp Ser Gln Gly Ile Lys Pro Ala Pro Phe Gln Asn
    50                  55                  60

Pro Thr His Glu Arg Glu Phe Ser
65                  70
```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 548 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
CCCAGGTTTA ATGATTTATT TAACTGGTGG GAACAAAAAT TAACCCAGAT TACCCACACC    60

CATGCCTAAC TTTATCAATT GTTTAGGAGG TAATTTTGAT TCTTATTTGA AAAAATGTTC   120

CATCCATTAT AAACAATTCC CAATAATCCG GTCAATTATT TTCCTAAATT TCCCCCCAAT   180

TCCTTAGGAG AGGATGTAAT TGGGAGGTAA CTTTTGGACG GCTTACTATC TTAACAAGNT   240

TGGGGTGAAG GGTTGAGGAG TCCAAACCCT TCCCAGATGG TGGGNGNNGG GTNAAGGAAT   300

TCCCTTTNTC CCCCCCCCCC NNNGGGGNCN GCCCCCCCCC NGGGNNCCCC CNGGGGGGAA   360

CCCNCTCCNG TTTNAANAAA AAANNGGGGG GAGAGNCCNA NAGCGGGGGT TTTTTTTGGG   420

GGGCCCCCCC CCCCCCNCCN AAANTTCTCC CCCCCNAGNG GGGGAAANNG NCNNCNCNTT   480

TTCACTNCNA CNNCTNCNCC NGCNNNGGGG GGGGGGTTCC CCCCCCCCNC NCGGGNCCCC   540

CCCCCCCC                                                            548
```

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 239 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```
TCCCCCAAGT CCAAATTTTT TTTTTCCTCT GATTGGGGAT GATTTTTAGG GGGAAGGGAA     60
ATTGATTTTC AAAAGGTTTT TTGGAAAATC CATTTAAATC CTGGTTTTTT CCTTAAAAGT    120
TTCAGAAAGG TAAAATTTTG AACTAAAAAG GAAGGGAGGC CGTAACAAGG TTTTGGGTGT    180
TGAGATTAAT TGAACAGGGA TTTTTAACAT GGTTTTGGTT TACAACTGGG GGAATANAA     239
```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 379 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
GGGTGATCAT GCACAAGTCT TAATTTATTG GGTAAAAACA TTAATTTATT ACAACATTTT     60
TCCCAATAAA GCATAATAAA TAGAATCCAT TTCTTTTAAA ACGCTGTACA AGAGACTGGA    120
AAACAAGCTC CCAACAGAAT ATGAATAACT CATAACTCAT CCTACCTTCT TATTGATTGG    180
GGACGCTCCC CCCACCCCCC ATGCCTGAAG CAACGTGCAC ACTTCAGGTC TCTGARCACA    240
GCCGGCCAAG GCCACCAGCT TCTAGGSTCC CTGGAGGTCA TGACTTCACT CTTAAATGCT    300
CTGCCCTTGG GTCTCGTCTT AGGCCCAGGA GGCTGAGGGC AGGAGAACTG ACCCGTTAGG    360
TGGTTGTGGC CTGGAGGAG                                                 379
```

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 296 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATCAGTCTGA TGTAGCTTTT ATTGAGTAAA GGAAAAAGGG AATTCAGCCG CATGATACAG 60

AGGTTCCAGT TGATCAGAGT GCGCAAACAC CCTTCCTGTC TGCGTGATGG GAACCGCACC 120

AGCACACGGG GTACGCGGAA GCCACTGCCG CAAGGAGATG GTTCCCACTC TCACGCACAT 180

GAGCAGCTCC TGGTCAGTCC CAAGAGGCAA GGGCAGAGGG CATGGTGGCT CTCACAGAGC 240

TACTTTACAA ATAAACTGTG TGTCTTCCTC AGGAGTCTCT TACAACACTT TTAAAA 296

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 365 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

AACTATTTTA ATTAGAATTT TTATTTGGTG CTTCAGGGCC ACAGGATAAA ATAACTACAT 60

TTAGCTTGCC TTTCAGTGAC GCTTTGGCCA AATGTCAGCT ACAAGGAGTC ATCTCCCTCA 120

CCGCCAAGCT GTCTAGCAGC CAGAGTGGTA GCTTTACTGT AACACACAGT ACTTTTGGTA 180

ATCAGACTCA AAGTCTTCAT CCATACTGCT TGTGTCTGCC ATCTTTTGGG CATCAGTCTT 240

GGGCAGAAAT TGTGCATAGT CTATCCCCTG CTGCTCATAG AAAAGATTGT AGGCAGAGTC 300

GGGTGTCAAT TTCATCCGGG TGAAGTTCCT TACAGCTGCT GTCATTGTAC AAGTACCACT 360

TGCAG 365

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 339 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CCAGAATACC AAACACACCT TTATCCAGGT GGAAGTACAA AAGCACATCC CTAAACCAAA 60

CGCATACATG TGATTTTTAC ATTTCCTGTT TTTTAGGGAT TACATAATCC TGTTTCAGTC 120

ACCATACGTG ACTACTGGTC TCTATACATA AGGGTATACA TGTTGGACAG GAAAAAACAC 180

ATGCATTTTC CATTGGCTTT TACATTTRGA TCACTCCATT TATTTTTCAA TTTCATTTAG 240

ATTCCTACCT GGCCTGGATG AAATCCTACT CTKGCTGATG GCAAAGAAGT AAAATATAGT 300

GGCAGAACTA TCCTAGAGGG TTAGCCATAG GGGGATTAT 339

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 529 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

AGCCATAGGA GTTATAGAGT GAGCAACATA TTTGTATGTA TTTGTTGAGG GTCCCTACTG 60

AATATTATAA CACTGCAACT ATGAAAGCCT CAATTGCTGG ACTGACAACA AGAATTTTAA 120

ATAACATTTG TCTTACTCAC AAAATGTTAT AAAGCTTAAG ATGGAAAAAT ACAAAATGTT 180

GGGACATTAC CTAAAGAATC ATGAACTCTT GTTAGGTATA TGATGGTGGC CCTGAACTTG 240

AGCCAACATC TTGTAATCAC TTTTATCAGT CAAAAAGCCA TGTTCTTTTA TATAGCCTGT 300

AGACTATTAA AATACAAAAA TGTGGTAATG GATAAACAAC TATACACAAA GCCCTCACAC 360

TTCAAATACT GTCCTGGATT GATGAGAGAG GAGCAGAATT CAACCATTTA TCTGCAATCC 420

TAATGGGTAA AATTTTACCA GGAACAGACC TGCACTCTCT GAATACTGCT CTGAGATTAC 480

ATACGACAGG ATCATCTCTT GTTGGGAGGC TACATCCCCT ATGAGCGAT 529

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 386 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

GGCTGTTAAA TAACTTTAAT GGTTGATGTG GGAGTCACAA GGGAGGTATG TTGGCTCCAA 60

GGGTTCTCCA GTGCCATCCT CAAAGCTGGT TAGTGAAGGG AGGTAGGGAA GAGTTGGTTC 120

CAGTTTTCTC CCAGGAAGGG TTTAGGGAGG TCCCAGCGAG CCCCAGGAAT GAGTCCCTCG 180

GTACCATGGA AACCACAATT TAAGAGGGGC TTCTGCCCAC CCCTGCAGCC TACCCCAGGT 240

CCAGCAGAGG AACAGGAGGC CAGACTGGCC AACTTGCTAT AGACAGCGCC GTATCCAGAG 300

CCCAACTGCG CATGGGTCAT TTTCTCTTCT GGGCAGATCC TATGCCAGAC CTTCTCTCTC 360

ACACTGGTGA CTTGGAGCCA AGTGCG 386

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 306 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

AAGGTGAAAG TTGGCTATTT ATTTAGTCTT AGAAAAACAC TGAAAGAAAA AGGCAGGAAA 60

TGTAGTACGC AGTGTGGGAA GAATGGGGGC TGGCCACATG TAGTTTTAGC AAGCTGCAGA 120

GGAAACCTGG CTGAGTTCTA AGGTTACAAT TTTTCTTGTT CAGGAAGGGG TTTCCAAGGG 180

GAATACCTCT CATGATGGAC GGGAGCCAAT CCCGGTAACC CACCCCGGGT TTCCCGGGGG 240

GGTAACTTTG GGAAACCCAT GGCCTGGAAT CCTCATCTTT CCTGGGAAGG GGCATCCCCA 300

GGGGAA 306

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 471 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CTGCGAAAGC CGAACTTTTT TGGGGGTTTC CCACCTAAGA AGTTCCCAGT TGAGTTGAAT 60

GAAATGTGAA AAAGTCCCCT AGAAAGTTGG GCCTCGCAGT GTGTAAAAAA GGCCCCCCAT 120

GGGGAAGAGC CGTGAAACCA TTTTAAAAAA AGAGAAAGTG AGAGAGAATT CAGGCCCCCT 180

GGGAGCCTGG TTTGGGTGGA GTGAACATCG TTCAGGCCGG CCCATGTGCC AGGCCACTCC 240

TGTTGGTTCG GGGGCTGTTT TCTTCTCTAA TTGTGCTTTC CCNNCCAAGT CCTAAAANCT 300

CTGGGGTTGN GGCCACCAGA NAGACCAGAC CAANTCCCCG GGGTNAAGAG GGTTTNTTNC 360

CTNGGCGAAG TTGGNGGTGC CCCAAAAAAG NNACCCNAAA AANTNTTCCC CCCTTTCAGC 420

CCCCCNGANN CAAGGTTCCC TGGCNNGANC CCCCAACCCT NTTTCCCACC C 471

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 463 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

ATACAAAATT TATTATTATA TTTTATTCAG GATGACAAGC CATCAGGAGG TCAACAACAC 60

AAGCACAGAC AGAGGGAAAG AGGGCAACCT GCTGAATGTC AGGGGCTGTC TTGAGGGGTT 120

GAGGGTTCCG CCCTCGGGAG GGTTGAGGAA GAGGGAAGGG AACCGGCAAG GATTCAAGTT 180

CCCCCCCTCC CGAGGGGTAA CCCTCCCCTC CTAAGGAGAA AAGTTGAGGG ATGTGAGAGG 240

CCTTTAACCC GTGCGGAGAT CTCTGTGGTG CCCCCCCAGT TGGNCTCATT TNCATTTGGG 300

GGACAACCCC CACACCCATA NGNTNGNNGT NCCCNCGNGG TCTTGNGAGG NCCCNTNNGG 360

NCGCCAAGGA ANNGCCCCAA AAGAAGATNT TCACCCTNTC ATTGNTTNAA GGAAGTCCCN 420

TGGGNNNNGC CGCCTCTTTT TTTCNTTGGG CCCCTCCCNN CCC 463

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 392 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GAATTCGGCA CGAGGTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTGAAT GGGGTTATCC 60

AGGATGTGAC TTTGGGAGAT TGGTTTTTTC CGTGGATTAT CCTGCCCCTG AGATCCACCC 120

AAGTTGTGGG ATCTGAAACT GGCCCACCCT CCGGGATTTT GAAGGACGCT GAATCATGAG 180

CGACAGTAAT TGTGAAAGCC AGTTTTTTGG TGTGAAAGTG GAAGACTCAA CCTCCACTTG 240

TCCTAAAACG GTTACCAGAA GTTGAACCCA ATTGGTTCCT GGGGCCCAAG GGATTGTTGG 300

GTGTTGCATT GGGTACAGCC CTTGGGATAA TTGTTGGAGG CCAAGAAATT AGGCCCCCCT 360

TTCCAGACCC AACTCATGAA AGGGAGTTCT CC 392

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 506 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

TTGACCAAAC CTCTGGCGAA GAAGTCCAAA GCTTCTCGAG GGCCAACAGG GCCCCTTTCT 60

CCCACAGGCC CGGCCTCTCC AGGTTGTCCC TGAGGACCCT GGGGTCCCAG GGGGCCCAAG 120

CTGCCGGGGT CTCCTTTCGG GCCTCTGCCG CCAACAGGCC CTTTCACGCC CATATCTCCT 180

TGGAATCCTC TTGGTCCTGG AGGGCCGGGG GCACCTCGTA GGATGGTGAC ATTGCGAAGG 240

ATTTCTCCAT GCTGTGTGTC CACTGCCTTC ATCTCCTCCA CGATCATGGA GAGGTTCCGG 300

ACGTTGAGGT CCAGCCGGGC ACTGAGCAGG CTGAAGCGCT CCCGGAGCAG GTCTGTGGTG 360

CCCAGCATGA TGGAGACAGA CTTGTTCAGG TAGTAGAGCT CCTCGGCATG GGTGTGGAAG 420

CCCAGCGTGC AGGAGAGCCG AACGTCATCC AGGTACTTGG AGCATGTTGT GCACGTGGTG 480

GTCGGTGGAA TTGATGTTGG TGAAGA 506

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 474 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CCAAAGGCAT TCAGGCTCTT TAATGTCTGA GGATGGGGGG AAGAAGTCAA TGGTGAGGCT 60

CCTCTGGGAA ATTCTGAAGG CCTGGTGGTT CTCTAAGCCC CTCTAGCAAC ATGTGGATAT 120

GGGCTTGGAT ATCCATGGAG TCCTTGGTGA GGCTGTTGCT GAGCTCTGTG AGGAGAGAGC 180

TCTTACGACC AATGAACTGG AGAGCTTCTG CCAGTGTCAC CTCCAGGAAA AAACCATATC 240

CCAGGGCCAC ATAGATGCGT GAAGTATCTG GGACCACTGT GTCAACGAAG AAGTTACAGC 300

CCAAATCCAC CTGCATATAT AACTCCGAGT GCTTAGCTTC CTGGAGTCGC TCAATGACAT 360

TTCTCAGTTG AGGGTATTTG GCCAGCTGTT CATATACCTG GTCTCGATGG TCCAGAACTT 420

TCGGAAGTCC CGCTGCAGAA CGTCACTGAT GAAGGGCTCG TGGGGAGAAT TTCT 474

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 454 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

TGGCATCTGA AATCTTTTAT TGGAAGATCA TTGTTGTTTG CCAATTAGAA GACACAGACA 60

GCAGACGAAC AGTGAAAACA GAGCCCAGTG ACGAGAGCCG GCCCCTTGGT TGGGGACCCT 120

CCCCAACTAC CTGGTAGACC AGCCTGGTGA CCTCTGCCCT TCCCCGGACC CCCGGGCCTT 180

TGGCATAATG CTGATGGGGG GCTGCAGGCA GTGAAGCCCC TTGACTCAAA GCAGAGACTT 240

GATTGGGCGC TGGAGAGTGG AGACAGTGGA GAGGCCAGGG AGGGCTGGGC GGGCCCCCCA 300

GGCTGGGCCG AGCAGCGCAA GTAGAGGAAG TCAGGAGCGG GCGAGATGGC ATCTATCTTG 360

TTTTCTTGAA AAGGGGGCAC ATAGGGGGCC TGGGAAGCAG GTGGCGGGTG GGTAGCTTGG 420

GGAAGGTCAA CACACTGAAC ATCCTTCTTC ATCG 454

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 307 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

AGTGATTATG CTTTTATTTA TTTCCAACTT CTTATGGGTA ACATAATTTC CAGACAATGT 60

TAGCTGTTTT TAATCCATCA GTAAACTGCA TTAAGATTCT TAATAAACAA ACACTGANGG 120

CCTCTTCCAT ATTGGTTTCA TCTGCATTTT TTTTTATATG CTGGTCATGT GGCTTTACTT 180

TCAGCCTCAC TCTTTTCTTC TTCCAAATGG ATTATCCTTA AACCTTTTAC CTTTAAAGAG 240

CCTGAGATTT ATATTTAACT CGAACAACAG TTGGGCTCTG TTGGCCCTGT GTTCATGTTT 300

TCCTAAG 307

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 319 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

CCCCCTTTAA GTGTTACACT TTTTTTTAAA ACTTAACATT TCAGGAGGTC ATACGCATAC 60

ACCTCAAACT GCAAAAAATT CCAGGCATAA AAACTATTAT CTGGGTTAGT GTGCCATCTT 120

TCTTCTCCAA ATGTCAAACT GTCCACAAAA AAAGTCTTAA GAAAGTCAAT TCCACTGTCC 180

ATTGGTGTGG GGTAAGAAAC CTATGTCTCA TCCACTGCAT GGAATCCATG TTAAAAGAAC 240

CCTGCCTTGG TTGTTTATCA TCACAGGACT CTTGTGTTAA TCCATTCTCC CTCAATTCCC 300

CACAGTAGAC TGCCATCTT 319

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 504 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GAATTCTGCG GCCGCCTCCT GAGCAAAAGC CCATCCTCAC TCAGCGCTAA CATCATCAGC 60

AGCCCGAAAG GTTCTCCTTC TTCATCAAGA AAAAGTGGAA CCAGCTGTCC CTCCAGCAAA 120

AACAGCAGCC CTAATAGCAG CCCACGGACT TTGGGGAGGA GCAAAGGGAG GCTCCGGCTG 180

CCCCAGATTG GCAGCAAAAA TAAACTGTCA AGTAGTAAAG AGAACTTGGA TGCCAGCAAA 240

GAAAATGGGG CTGGGCAGAT ATGTGAGCTG GCTGACGCCT TGAGTCGAGG GCATGTGCTG 300

GGGGGCAGCC AACCAGAGTT GGGTCACTCC TCAGGACCAT GAGGTAGCTT TGGGCCAATG 360

GATTCCTTTA TGAGCATGAG GAATGTAGCA ATGGTTACAG CAATGGTCAG CTTGGAACCA 420

CAGTGAGGAG AAAGCACTGA TGACCAAGAG GAGATCTTCG TTTAAGCCTA TTTATATCTA 480

TATGAATTCG GGCAATCAGA TTCT 504

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 504 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GAATTCTGCG GCCGCCTCCT GAGCAAAAGC CCATCCTCAC TCAGCGCTAA CATCATCAGC 60

AGCCCGAAAG GTTCTCCTTC TTCATCAAGA AAAAGTGGAA CCAGCTGTCC CTCCAGCAAA 120

AACAGCAGCC CTAATAGCAG CCCACGGACT TTGGGGAGGA GCAAAGGGAG GCTCCGGCTG 180

CCCCAGATTG GCAGCAAAAA TAAACTGTCA AGTAGTAAAG AGAACTTGGA TGCCAGCAAA 240

GAAAATGGGG CTGGGCAGAT ATGTGAGCTG GCTGACGCCT TGAGTCGAGG GCATGTGCTG 300

GGGGGCAGCC AACCAGAGTT GGGTCACTCC TCAGGACCAT GAGGTAGCTT TGGGCCAATG 360

GATTCCTTTA TGAGCATGAG GAATGTAGCA ATGGTTACAG CAATGGTCAG CTTGGAACCA 420

CAGTGAGGAG AAAGCACTGA TGACCAAGAG GAGATCTTCG TTTAAGCCTA TTTATATCTA 480

TATGAATTCG GGCAATCAGA TTCT 504

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 365 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

AACTATTTTA ATTAGAATTT TTATTTGGTG CTTCAGGGCC ACAGGATAAA ATAACTACAT 60

TTAGCTTGCC TTTCAGTGAC GCTTTGGCCA AATGTCAGCT ACAAGGAGTC ATCTCCCTCA 120

CCGCCAAGCT GTCTAGCAGC CAGAGTGGTA GCTTTACTGT AACACACAGT ACTTTTGGTA 180

ATCAGACTCA AAGTCTTCAT CCATACTGCT TGTGTCTGCC ATCTTTTGGG CATCAGTCTT 240

GGGCAGAAAT TGTGCATAGT CTATCCCCTG CTGCTCATAG AAAAGATTGT AGGCAGAGTC 300

GGGTGTCAAT TTCATCCGGG TGAAGTTCCT TACAGCTGCT GTCATTGTAC AAGTACCACT 360

TGCAG 365

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 444 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

GAATTCTGCG GCCGNCGGGC ACAGGCAGTG CTGGAGGAAG ACCACTACGG GATGGAGGAC 60

GTCAGGAAAC GCATCCTGGA GTTCATNGCC GTTAGCCAGC TCCGCGGNTC CACCCAGGGC 120

AAGATCCTCT GCTTCTATGG CCCCCCTGGC GTGGGTAAGA CCAGCATTGG TCGCTCCATC 180

GNCCGCGCCT GACCGAGAGT ACTTCCCGCT TCAGNGTCGG GGGGATTATG ACGTNGGTGA 240

GATCAAAGGG CACAGGGGGC CTCCGTGGGC GCCATTCCGG AAGATCATCC ANTNTTGGGG 300

AAGACCAAAN GGNGAACCCC TTATTCCNCA TCGAGAAGGN GGNAAAAATC GNCCANGTTA 360

CNAGGGGCCC CCNNNTCGNA ATTNTTNTGT TTTTTTACCA ANAAAAATNT CATTTCCCNG 420

ACCNTNCTGG GGGTCCCCTN ANTT 444

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 423 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

ACTGAAAATG ACTTTAATCA TTAAATAGCT TCTATGCCAC ACTCTGATTA AGCCGACTGA 60

GGTCCCTGGG ATCTGGGTCA CTGGACCGAG CTGCTCGCTC GGTGGCTCCA CTGCCAGGTC 120

CGGGCGCGCT CCCCACAGGG GTCAGTCTTG GCCAGACAGG GCTGANATCC GCGCCTGAAG 180

TCCGGGTGGG CCGCACCGTC CACGGCAGGG CTCTGCTTTC GCCGGGAGGG GAAGTCGAGG 240

TCTCCCGNNG GGTCCAGAAG GGGAACCCCA GGCCCCGGGG ATNAANGTNC CAGGCGGGAA 300

AGTCCCCTTT TCTCNGTTGG AANAAAAAAA AANAACCCCN NGNGCTTGGG NNAAAGGCCT 360

NCTCCTGGNG GNCNACANAN NAAGATNTTN CCCGNGGGGG ATTCCCCAAA NAAANCAAAT 420

TTT 423

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TACCAGCCTC TTGCTGAGTG GAGA 24

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TAGACAAGCC GACAACCTTG ATTG 24

1. A substantially pure preparation of a CDK4-binding protein, or a fragment thereof, comprising an amino acid sequence at least 60% homologous to a polypeptide selected from a group consisting of SEQ ID Nos. 25-48.

2. A preparation of a purified or recombinant polypeptide comprising an amino acid sequence identical or homologous to a sequence of SEQ ID No. 31, which polypeptide binds to a cyclin dependent kinase.

3. The preparation of claim 2, which polypeptide functions in one of either role of an agonist or an antagonist of cell cycle regulation by a cyclin-dependent kinase (CDK).

4. The preparation of claim 2, which polypeptide has a proteolytic activity.

5. The preparation of claim 4, which polypeptide binds CDK4.

6. The preparation of claim 4, which polypeptide is a fusion protein.

7. A preparation of a purified or recombinant polypeptide comprising an amino acid sequence identical or homologous to a sequence of SEQ ID No. 33, which polypeptide binds to a cyclin dependent kinase.

8. The preparation of claim 7, which polypeptide functions in one of either role of an agonist or an antagonist of cell cycle regulation by cyclin-dependent kinase (CDK).

9. The preparation of claim 7, which polypeptide has an isopeptidase activity.

10. The preparation of claim 9, which polypeptide is a de-ubiquitinating enzyme.

11. The preparation of claim 7, which polypeptide is a fusion protein.

12. A preparation of a purified or recombinant polypeptide comprising an amino acid sequence identical or homologous to a sequence of SEQ ID No. 43, which polypeptide binds to a cyclin dependent kinase.

13. The preparation of claim 12, which polypeptide functions in one of either role of an agonist or an antagonist of cell cycle regulation by a cyclin-dependent kinase (CDK).

14. The preparation of claim 12, which polypeptide has a kinase activity.

15. The preparation of claim 14, which polypeptide is a stress-activated protein kinase.

16. The preparation of claim 12, which polypeptide is a fusion protein.

17. A preparation of a purified or recombinant polypeptide comprising an amino acid sequence identical or homologous to a sequence of SEQ ID No. 45, which polypeptide binds to a cyclin dependent kinase.

18. The preparation of claim 17, which polypeptide functions in one of either role of an agonist or an antagonist of cell cycle regulation by a cyclin-dependent kinase (CDK).

19. The preparation of claim 17, which polypeptide is cdc37 homolog.

20. The preparation of claim 17, which polypeptide binds CDK4.

21. The preparation of claim 17, which polypeptide is a fusion protein.

22. An antibody preparation specifically reactive with an epitope of the polypeptide of claim 1.

23. An antibody preparation specifically reactive with an epitope of the polypeptide of claim 2.

24. An antibody preparation specifically reactive with an epitope of the polypeptide of claim 7.

25. An antibody preparation specifically reactive with an epitope of the polypeptide of claim 12.

26. An antibody preparation specifically reactive with an epitope of the polypeptide of claim 17.

27. A polypeptide a recombinantly produced from a pJG4-5-CDKBP clone of ATCC deposit no. 75788.

28. An nucleic acid having a nucleotide sequence which encodes a polypeptide comprising an amino acid sequence identical or homologous to a sequence of one of SEQ ID No. 25-47, which polypeptide binds to a cyclin dependent kinase.

29. The nucleic acid of claim 28, wherein said polypeptide encoded by said nucleic acid functions in one of either role of an agonist of cell cycle regulation or an antagonist of cell cycle regulation.

30. The nucleic acid of claim 28, wherein said nucleotide sequence hybridizes under stringent conditions to a nucleic acid probe corresponding to at least 12 consecutive nucleotides of one of SEQ ID Nos. 1-24 and 49-70.

31. The nucleic acid of claim 28, wherein said polypeptide comprises an amino acid sequence identical or homologous to a sequence of SEQ ID No. 31.

32. The nucleic acid of claim 28, wherein said polypeptide comprises an amino acid sequence identical or homologous to a sequence of SEQ ID No. 33.

33. The nucleic acid of claim 28, wherein said polypeptide comprises an amino acid sequence identical or homologous to a sequence of SEQ ID No. 43.

34. The nucleic acid of claim 28, wherein said polypeptide comprises an amino acid sequence identical or homologous to a sequence of SEQ ID No. 45.

35. The nucleic acid of claim 28, wherein said polypeptide is a fusion protein.

36. The nucleic acid of claim 28, further comprising a transcriptional regulatory sequence operably linked to said nucleotide sequence so as to render said nucleotide sequence suitable for use as an expression vector.

37. An expression vector, capable of replicating in at least one of a prokaryotic cell and eukaryotic cell, comprising the nucleic acid of claim 36.

38. A host cell transfected with the expression vector of claim 37 and expressing said polypeptide.

39. A method of producing a recombinant CDK4-binding protein comprising culturing the cell of claim 38 in a cell culture medium to express said CDK4-binding protein and isolating said CDK4-binding protein from said cell culture.

40. A transgenic animal comprising cells harboring a recombinant form the nucleic acid of claim 28.

41. The nucleic acid of claim 28, which includes intronic nucleotide sequences disrupting said polypeptide-encoding sequence.

42. A nucleic acid composition comprising, as nucleic acid component, a substantially purified oligonucleotide, said oligonucleotide containing a region of nucleotide sequence which hybridizes under stringent conditions to at least 40 consecutive nucleotides of sense or antisense sequence selected from a group consisting of SEQ ID Nos. 1-24 and 49-70, or naturally occurring mutants thereof.

43. The nucleic acid composition of claim 42, which oligonucleotide hybridizes under stringent conditions to at least 80 consecutive nucleotides of sense or antisense sequenceselected from a group consisting of SEQ ID Nos. 1-24 and 49-70, or naturally occurring mutants thereof.

44. The nucleic acid composition of claim 42, which oligonucleotide further comprises a label group attached thereto and able to be detected.

45. The nucleic acid composition of claim 42, which oligonucleotide has at least one non-hydrolyzable bond between two adjacent nucleotide subunits.

46. A diagnostic test kit for identifying an transformed cells, comprising the nucleic acid of claim 42, for measuring a level of a nucleic acid encoding a CDK-binding protein in a sample of cells isolated from a patient.

47. An assay for screening test compounds for an inhibitor of an interaction of a cyclin dependent kinase (CDK) with a CDK4-binding protein (CDK-BP) comprising
    i. combining a CDK and a CDK4-binding protein, which CDK4-binding protein includes an amino acid sequence represented in a group consisting of SEQ ID Nos. 25-48, under conditions wherein said CDK and said CDK4-binding protein are able to interact;
    ii. contacting said combination with a test compound; and

iii. detecting the formation of a complex comprising said CDK and said CDK4-binding protein,

wherein a statistically signficant decrease in the formation of said complex in the presence of said test compound is indicative of an inhibitor of the interaction between said CDK and said CDK4-binding protein.

48. A method of identifying an agent which disrupts the ability of a CDK4-binding protein to regulate a eukaryotic cell cycle, comprising:

i. providing an interaction trap assay system including a first fusion protein comprising a cyclin-dependent kinase (CDK) and second fusion protein comprising a CDK4-binding protein including an amino acid sequence selected from a group consisting of SEQ ID Nos. 25-48, under conditions wherein said interaction trap assay is sensitive to interactions between the CDK of said first fusion protein and said CDK4-binding protein of said second polypeptide;
ii. contacting said interaction trap assay with a candidate agent;
iii. measuring a level of interactions between said fusion proteins in the presence of said candidate agent; and
iv. comparing the level of interaction of said fusion proteins in the presence of said candidate agent to a level of interaction of said fusion proteins in the absence of the candidate agent,

wherein a decrease in the level of interaction in the presence of said candidate agent is indicative of inhibition of an interaction between said CDK and said CDK-binding protein.

49. A method of determining if a subject is at risk for a disorder characterized by unwanted cell proliferation, comprising detecting, in a tissue of said subject, the presence or absence of a genetic lesion characterized by at least one of

a mutation of a gene encoding a protein selected from a group consisting of SEQ ID Nos. 25-48, or homologs thereof; and the mis-expression of said gene.

50. The method of claim 49, wherein detecting said genetic lesion comprises ascertaining the existence of at least one of

i. a deletion of one or more nucleotides from said gene,
ii. an addition of one or more nucleotides to said gene,
iii. an substitution of one or more nucleotides of said gene,
iv. a gross chromosomal rearrangement of said gene.
v. a gross alteration in the level of a messanger RNA transcript of said gene,

vi. the presence of a non-wild type splicing pattern of a messenger RNA transcript of said gene, and
vii. a non-wild type level of said protein.

51. The method of claim 49, wherein detecting said genetic lesion comprises
    i. providing a probe/primer comprising an oligonucleotide containing a region of nucleotide sequence which hybridizes to a sense or antisense sequence of nucleic acid of one of SEQ ID Nos. 1-24 and 49-70, or naturally occurring mutants thereof, or 5' or 3' flanking sequences naturally associated with said gene;
    ii. exposing said probe/primer to nucleic acid of said tissue; and
    iii. detecting, by hybridization of said probe/primer to said nucleic acid, the presence or absence of said genetic lesion.

52. The method of claim 49, wherein detecting said lesion comprises utilizing said probe/primer to determine the nucleotide sequence of said gene and, optionally, of said flanking nucleic acid sequences.

53. The method of claim 49, wherein detecting said lesion comprises utilizing said probe/primer to in a polymerase chain reaction (PCR) or ligation chain reaction (LCR).

54. The method of claim 50, wherein the level of said protein is detected in an immunoassay.

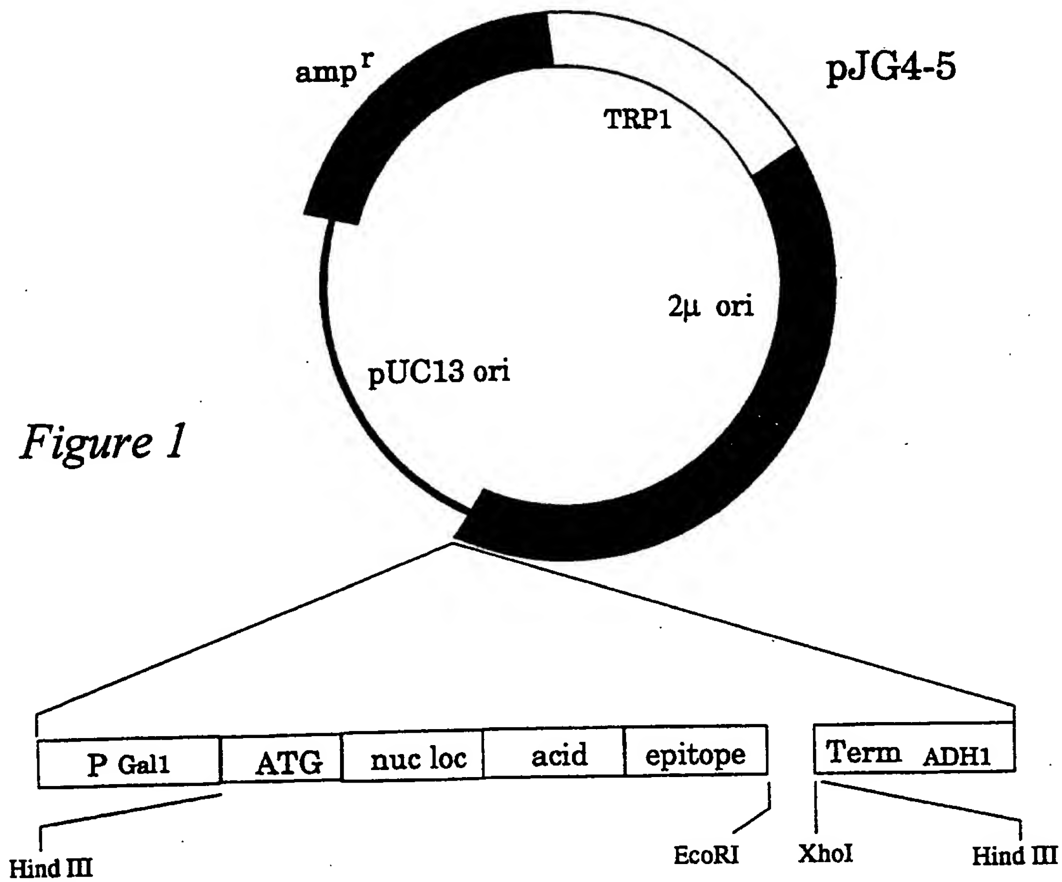

Figure 1

AAG CTT ATG GGT GCT CCT CCA AAA AAG AAG AGA AAG GTA GCT GGT
M G A P P K K K R K V A G

ATC AAT AAA GAT ATC GAG GAG TGC AAT GCC ATC ATT GAG CAG TTT
I N K D I E E C N A I I E Q F

ATC GACTAC CTG CGC ACC GGA CAG GAG ATG CCG ATG GAA ATG GCG
I D Y L R T G Q E M P M E M A

GAT CAG GCGATT AAC GTG GTG CCG GGC ATG ACG CCG AAA ACC ATT
D Q A I N V V P G M T P K T I

CTT CAC GCC GGGCCG CCG ATC CAG CCT GAC TGG CTG AAA TCG AAT
L H A G P P I Q P D W L K S N

GGT TTT CAT GAA ATTGAA GCG GAT GTT AAC GAT ACC AGC CTC TTG
G F H E I E A D V N D T S L L

CTG AGT GGA GAT GCC TCCTAC CCT TAT GAT GTG CCA GAT TAT GCC
L S G D A S Y P Y D V P D Y A

Figure 2

pjG4-5 clone	CDK2	CDK3	CDK4	CDK5	CDK6	cdi1	Rb	ΔRb	p53	cycC	cycD1	cycD2	cycE
#11			+++	+	++								
#13			+++	+++	+++								
#22			+++	+			+	+	++				
#36			++				+	+	+				
#61			++	+	+								
#68			+++	+	+++								
#71			+++	+	+								
#75			++										
#116			++		+		++	++	+++				
#118			++										
#121			++										
#125			++			+	+	+	++				
#127			+++				+++	+++	+++				
#165			++				+	+	+				
#166			+		+		++	+	+				
#190			+				+	+	+++				
#193			+		+		+	+	++				
#216			+		+		+/-	+/-	+/-				
#225			+		+	+							
#227			+		+								
#267			+		+								
#269			+		+/-		++	++	+++				
#295			+		+		+/-	+/-					
#297			+		+		+/-	+/-	+/-				
Cyclin D1	++	++	+++	+	++								
Cyclin D3	+++	+++	+++		+++								
p16			+++		+++								
p21	+++	+++	+		+						++	++	

Figure 3

cDNA	spln	thy	pros	tes	ov	s.i.	co	p.b.	he	br	pla	lu	lvr	s.m.	ki	pa	mRNA size (kb)
cyclin B1	+/-	+++	--	+++	+	+	+	+/-	+/-	+	+	+/-	--	--	+	--	
actin	+++	+++	+++	++	+++	+++	+++	+++	+	+	++	+++	++	+++	+++	+	
#11	+	+	--	--	+	+	+	--	--	--	+++	+	--	+	+	--	1.2
#13	+++	+++	+++	+++	+++	+++	+++	+++	+	+	+	+	+	+++	+	+	1.3
	+/-	+	++	+	+++	+	++	--	--	--	--	--	--	--	--	--	3.3
	--	+	++	+	+++	+	++	--	--	--	--	--	--	--	--	--	5.0
#22	++	++	+	++	+	+	+	+++	+	+	++	+	+	+	+	+	8.4
	++	++	+	--	+	+	+	+++	+	+	++	+	+	+	+	+	9.5
#36	+++	+++	+++	+	+++	+++	+++	+++	+++	+	++	+++	++	++	++	++	1.3
#61	+/-	+/-	+/-	+/-	+/-	+/-	+/-	--	+	+/-	+++	+	++	++	+++	+++	9.5
	--	--	--	--	+/-	+/-	+/-	--	++	++	++	+	--	+	++	+	5.5
#68	+	++	--	+	--	--	--	+++	+	++	--	+	--	+	+/-	+	1.2
#71	+	+	+	+	++	+	+++	+	+	+	+	++	++	+++	++	+	3.0
#75	++	++	++	+++	++	++	+	+++	++	++	++	+++	+++	+	++	+	2.1
#118	++	+++	++	++	++	++	++	++	+	+	+	+	+	+	+	+	5.5
#121	+	+	++	--	+	++	++	--	--	++	--	--	++	--	++	--	2.4
#125	+	+	++	+	+++	+++	+++	--	++	--	+	+	--	+	+	+	3.7
	--	--	+	--	+++	+++	+++	--	++	--	--	--	--	--	--	--	5.0
#127	--	--	--	+/-	--	--	--	--	--	--	+++	+	==	+	+	==	3.9
#165	+/-	+	+	+	+	+/-	+/-	+/-	+++	++	++	+++	+	+++	++	+++	1.1
#166	++	++	++	++	++	++	++	++	+++	++	+++	++	++	++	++	+++	1.3
#216	+	++	+	++	++	+	+	+	++	++	++	+	+	+++	++	++	8.0
#225	++	++	++	++	++	++	++	++	+	+++	+	+	+	+++	+	++	4.0
	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-	--	--	+	+/-	+	3.0
	++	++	++	++	++	++	++	++	++	++	++	++	+	++	++	+++	2.0

Figure 3 (con't)

#267	+	+	+	++	++	+	+	+	+++	++	++	+++	+++	+++	++	+++	1.6
#269	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	2.4
	++	++	++	++	++	++	++	++	--	+	+	++	+	+	+	++	7.0
#295	+	+	+	+	+	+	+	+	+	+	+	++	++	++	++	+	2.9
#297	+++	+++	+++	+++	+++	+++	+++	+++	+++	--	+++	+++	+++	+++	+++	+++	1.0

spln=spleen; thy=thymus; pros=prostate; tes=testis; ov= ovary; s.i.=small instestine; co=colon; p.b.= peripheral blood; he=heart; br=brain; pla=placenta; lu=lung; lvr=liver; s.m.=smooth muscle; ki=kidney; pa=pancreas